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ENONES AND ENALS AS LATENT ENOLATES IN CATALYTIC C-C BOND FORMING PROCESSES: TOTAL SYNTHESIS OF (-)-PAROXETINE (PAXIL®)

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by

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Dissertation

Presented to the Faculty of the Graduate School of

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Dedication

To my parents and my wife

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Publication No._____

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The University of Texas at Austin, 2007

Supervisor: Michael J. Krische

Enolates constitute one of the most commonly utilized intermediates in synthetic organic chemistry. However, the regioselective generation of enolates remains a challenge, especially for non-symmetric ketones possessing identical degrees of substitution at the α-positions. Our research has shown that regioselective enolate generation can be achieved by the activation of enones and enals with either 1) nucleophilic phosphine catalysis or 2) transition metal catalysis to generate enolates regioselectively. These enolates can be subsequently trapped with electrophiles.

Using nucleophilic phosphine catalysis we have developed the first method for the α-arylation of enones, enals, and nitroalkenes using bismuth(V) reagents. This phosphine-catalyzed arylation methodology is mild in that a strong base is not required. Additionally, the products of this reaction are easily elaborated to complex molecules.

This method has been strategically applied in a concise formal and enantioselective total synthesis of the blockbuster antidepressant (-)-paroxetine (PAXIL®).

In transition metal catalysis, we have used enantioselective Cu-catalyzed conjugate addition of Grignard reagents to enones to provide magnesium enolates, which can be arylated using bismuth(V) reagents to furnish products of vicinal difunctionalization of enones. These products are obtained in modest to good yields with complete control of both relative and absolute stereochemistry. Another method for regioselective enolate generation is the Rh-catalyzed hydrogenation of enones and enals. Using this method we have developed a reaction that involves addition of metallo-aldehyde enolates to ketone acceptors to afford aldol products. This is the first catalytic direct addition of transition metal enolates to ketones.

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Chapter 1: Historical Overview of Nucleophilic Catalysis *via* Conjugate Addition of Phosphines to Enones and Enoates

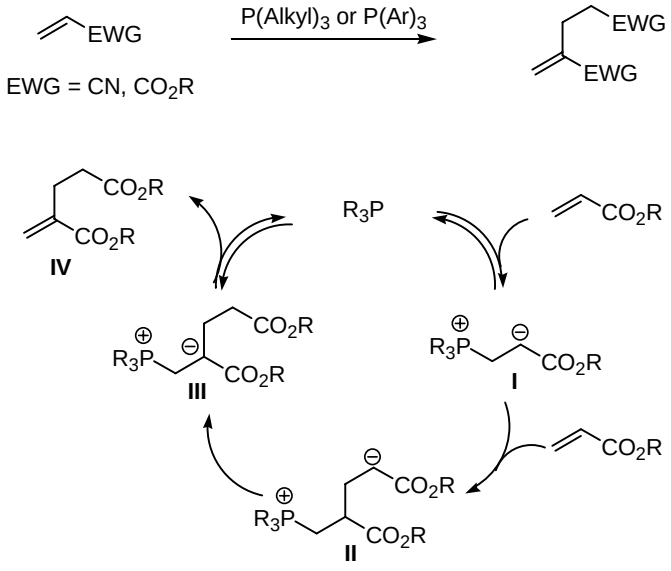
1.1 Introduction

Organocatalytic transformations have emerged as powerful methods for carbon–carbon bond formations.[1] Transformations based on nucleophilic activators form a distinct sub class of organocatalytic reactions.[2] Between 1960 and 1990 phosphines were not used extensively as nucleophiles. However, in the last decade reports on nucleophilic catalysis employing phosphine nucleophiles have increased dramatically. Conjugate addition of phosphine nucleophiles to activated alkenes provides intermediates that can be trapped by electrophiles resulting in new C-C bond formation. Tertiary phosphines and amines have pyramidal geometry, whereas phosphines are configurationally stable at above room temperature, tertiary amines undergo inversion at room temperature. This means phosphines retain chirality at phosphorus at room temperature which can potentially be exploited in asymmetric synthesis. In this account we present an overview of phosphine mediated reactions based on conjugate addition of *p*-nucleophiles to vinylic carbonyl and vinylic nitrile compounds.

1.2 Rauhut-Currier Reaction

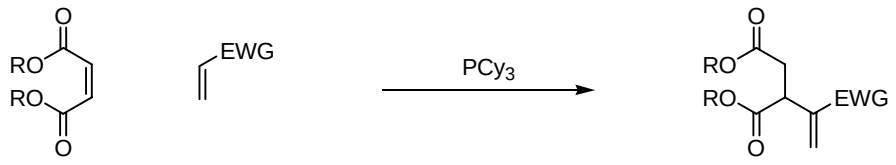
In 1963 Rauhut and Currier reported a phosphine-catalyzed dimerization of alkyl acrylates.[3] Later, in 1965 McClure,[4] Baizer and Anderson[5] independently reported a phosphine-catalyzed dimerization of acrylonitrile. This transformation is believed to proceed *via* reversible phosphine conjugate addition to an activated alkene to give a zwitterionic enolate **I**, which undergoes conjugate addition with a second activated alkene.

Proton transfer followed by elimination of the phosphine results in the dimer **IV** (Scheme 1.1).



Scheme 1.1 Mechanism for Rauhut-Currier reaction

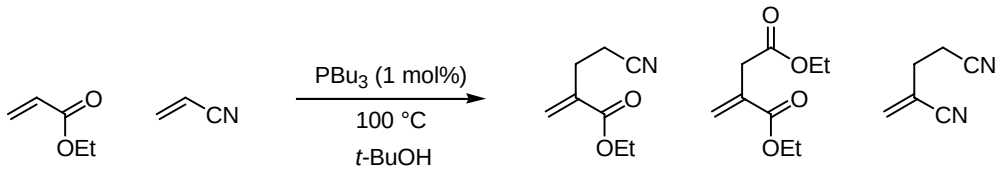
In 1969 Morita and Kobayashi reported a reaction between activated alkenes and fumaric/maleic esters catalyzed by tricyclohexylphosphine to provide product **1.3** (Scheme 1.2).[6] The first cross coupling reaction between acrylonitrile and acrylate was reported by McClure in 1970 (Scheme 1.3).[7] The cross coupling product **1.6** was obtained in 48% yield, along with products of homodimerization in 22-25% yield.



1.1 **1.2** **1.3**

EWG = CO_2Me, CO_2H, CN
R = H, Me, Bu

Scheme 1.2 Rauhut-Currier reaction of activated alkenes and fumaric/maleic esters

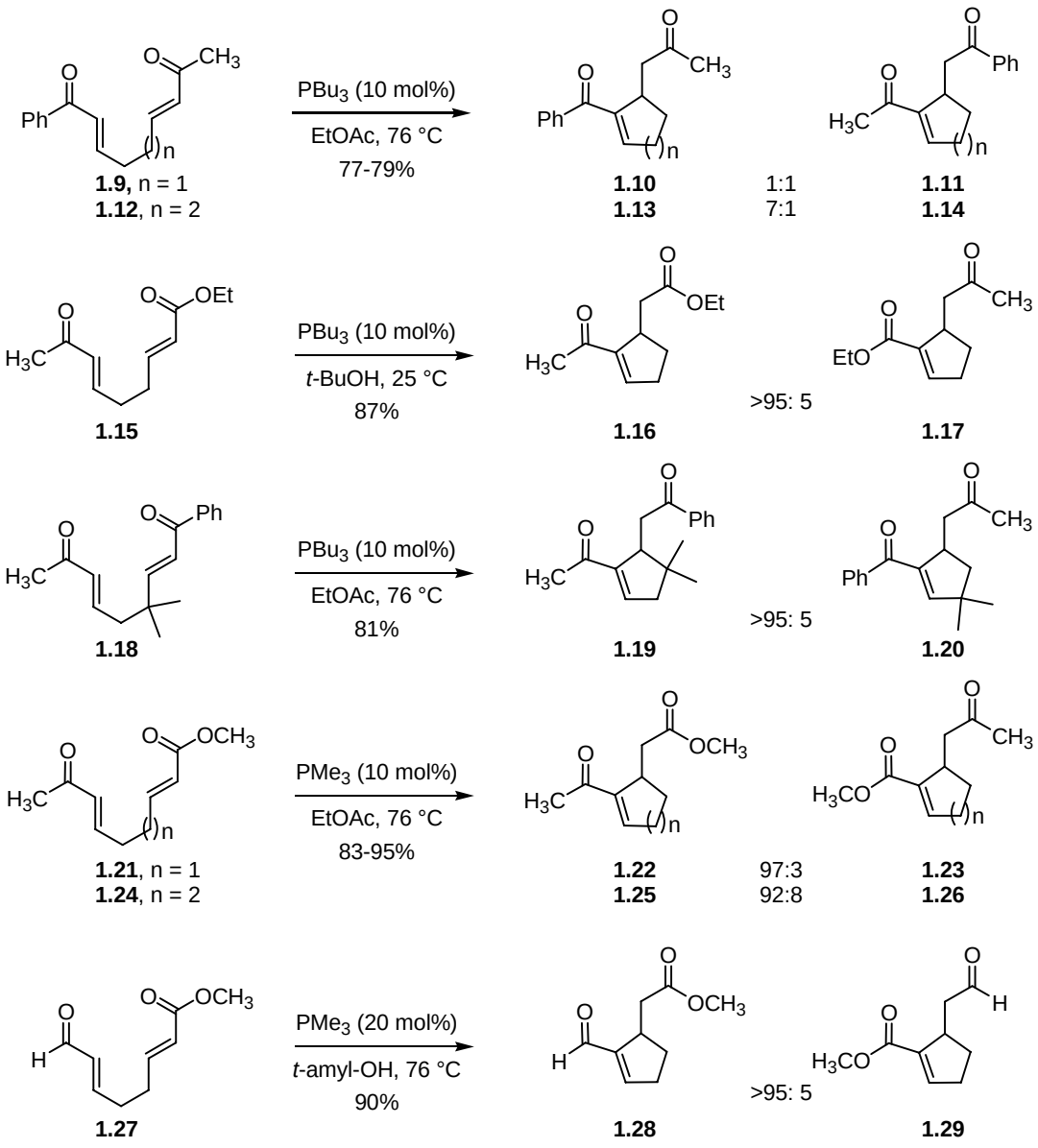


1.4 **1.5** **1.6**, 48% **1.7**, 22% **1.8**, 25%

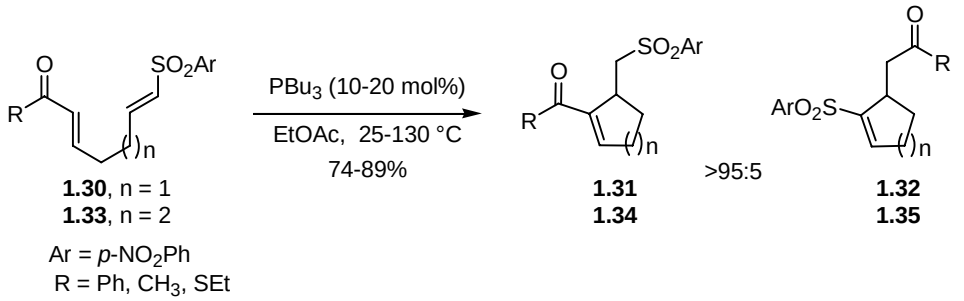
Scheme 1.3 First Cross Rauhut-Currier reaction

Three decades passed with very few reports of phosphine-catalyzed Rauhut-Currier reaction. During this period several groups reported tertiary amine-catalyzed variants of the Rauhut-Currier reaction.[8] In 2000, Jenner reported a phosphine-catalyzed dimerization of β-substituted acrylonitrile and acrylate under both ambient and high pressure.[9] The lack of selectivity in Rauhut-Currier reactions involving different activated alkenes remained a major limitation. Krische and Roush have concurrently addressed this problem through an intramolecular process, in which the activated alkene partners are tethered (Scheme 1.4).[10] Aromatic-aliphatic mixed bis(enone) **1.9** gives the cycloisomerization products **1.10** and **1.11** as a 1:1 mixture of isomers, whereas the homologous substrate **1.12** affords the cyclohexenes **1.13** and **1.14** in a 7:1 ratio, respectively. These data suggests that the kinetic phosphine adducts are trapped efficiently *via* cyclization to cyclopentene, but for cyclohexene formation, a slow cyclization rate enables a pre-equilibrium of tributylphosphine adducts. Unsymmetric

electronically biased bis(enones) undergo chemoselective cycloisomerization initiated by addition of the more electrophilic alkene onto the less electrophilic alkene as shown in substrates **1.15**, **1.21**, **1.24** and **1.27**. For substrates lacking significant electronic difference, steric factors direct chemoselectivity as demonstrated in substrate **1.18**. It was observed by both groups that tertiary amine nucleophiles such as DABCO, DBU, Et_2NH, and DMAP, which are common catalysts for Morita-Baylis Hillman reaction, were less effective in catalyzing intramolecular Rauhut-Currier reaction than the trialkylphosphine nucleophiles. This low reactivity is attributed to the fact that trialkylphosphines are more nucleophilic than the corresponding tertiary amines. Triarylphosphines are not viable catalysts for this transformation. In 2004 Krische and Luis reported that vinyl sulfones serve as effective Michael acceptors in phosphine-catalyzed intramolecular Rauhut-Currier type reaction, to provide cyclic products as single regioisomers (Scheme 1.5).[11]

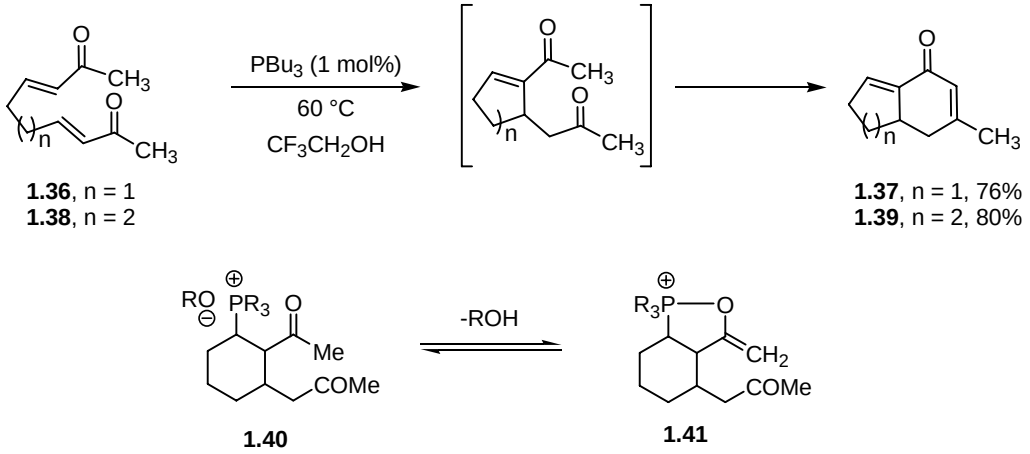


Scheme 1.4 Krische/ Roush intramolecular Rauhut-Currier reaction



Scheme 1.5 Enone-sulfone cycloisomerization

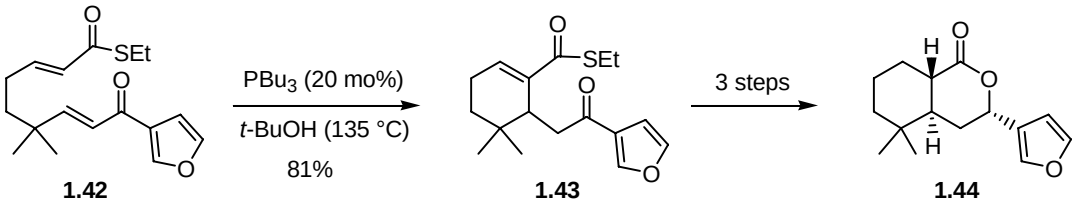
Recently Roush and Thalji reported a tandem Rauhut-Currier/aldol reaction that results in unprecedented chemoselectivity in the aldol step (Scheme 1.6).[12] Experimental data indicate that the phosphonium moiety of the phosphine-enone Michael adduct **1.40** controls the chemoselectivity. The phosphonium unit interacts with the adjacent carbonyl as seen in intermediate **1.40**, enhancing the acidity of the β-phosphonium-substituted methyl ketone promoting regioselective deprotonation by the alkoxide to provide enolate **1.41**.



Scheme 1.6 Rauhut-Currier/aldol reaction

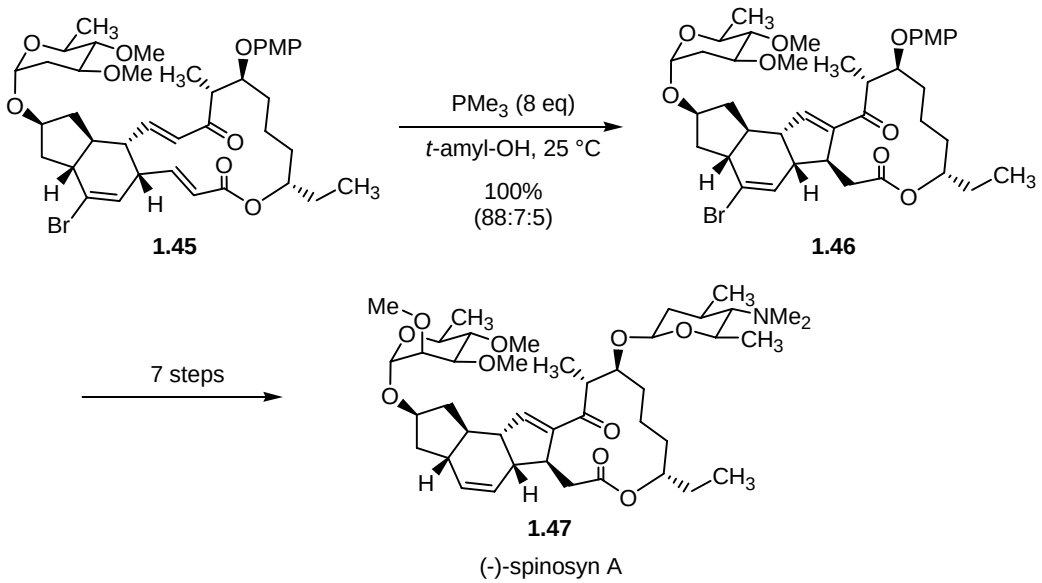
1.2.1 Application of Rauhut–Currier Reaction in Total Synthesis

In 2003 Krische and Agapiou showed that thioenoates participate in highly chemoselective phosphine-catalyzed cross Michael cycloisomerization with appendant aryl ketone and enoate partners to afford cyclopentene and cyclohexene products (Scheme 1.7).[13] This methodology was subsequently applied in a concise total synthesis of the furanosequiterpene lactone ricciocarpin A **1.44**.



Scheme 1.7 Enone-thioenoate cycloisomerization and total synthesis of (±)-ricciocarpin A

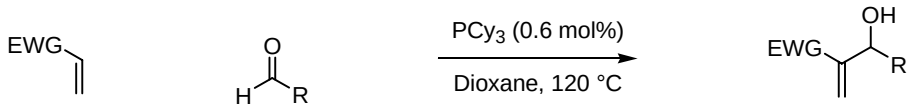
Roush and co-workers reported a transannular phosphine mediated Rauhut-Currier cyclization, also known as a vinylogous-Morita-Baylis-Hillman reaction, of the Diels-Alder adduct **1.45** en route to total synthesis of (-)-spinosyn A (Scheme 1.8).[14] The product of the transannular reaction **1.46** was elaborated to the desired natural product (-)-spinosyn A in seven steps.



Scheme 1.8 Transannular Rauhut-Currier reaction and total synthesis of (-)-spinosyn A

1.3 Morita-Baylis–Hillman Reactions

The phosphonium enolate intermediates generated *via* phosphine conjugate addition to activated alkenes can be captured by other electrophiles such as aldehydes. In 1968 Morita and co-workers reported the first reaction between acrylates and acrylonitrile with aldehydes in the presence of tricyclohexylphosphine to afford 2-(1-hydroxy-alkyl)acrylonitriles or -acrylates (Scheme 1.9).[15] Subsequent to this seminal result, in 1972 Baylis and Hillman reported a similar transformation using the tertiary amines such as DABCO, pyrrocoline, and quinuclidine.[16] This Morita-Baylis-Hillman reaction is an atom economical transformation for coupling activated alkenes, which include acrylic esters, acrylonitrile, vinyl ketones, phenyl vinyl sulfones, phenyl vinyl sulfonate esters, vinyl phosphonates and acrolein with a variety of electrophiles such as aliphatic, aromatic, and α-β-substituted aldehydes. The phosphine-catalyzed MBH reaction involving β-substituted activated alkenes requires more forcing conditions due to the slow conjugate addition of the phosphine to the alkene.



1.48 **1.49** **1.50**

EWG = CN, CO_2Me
R = Me, Et, *n*-Pr, *i*-Pr, Ph, *p*-Cl-C_6H_4, *P*-Me-C_6H_4

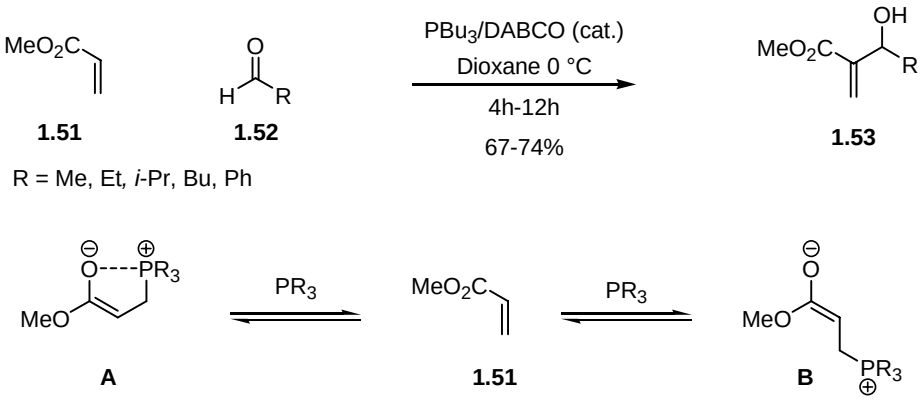
Scheme 1.9 Discovery of Morita-Baylis-Hillam reaction

Low conversion rate, substrate dependent chemical yields, and the susceptibility of the phosphine catalyst to undergo air-oxidation is a significant limitation of the Morita-Baylis-Hillman reaction when applied to complex synthetic problems. Based on

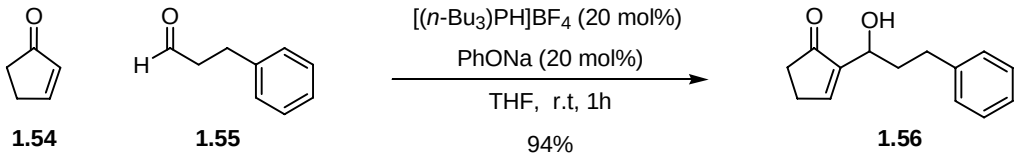
kinetic studies by Kaye and Bode the rate determining step is the trapping of the transient zwitterionic enolate by the aldehyde.[17] Due to these limitations the MBH reaction remained under developed for over a decade despite its synthetic potential. In the 1980s there was significant research activity in this area devoted to tertiary amine-catalyzed variants of MBH reaction.[2] Tertiary amines are cheaper and less toxic than trialkylphosphine catalysts, however phosphines give better yields in a shorter reaction time.

Kawanisi and co-workers improved the efficiency of the phosphine-catalyzed MBH reaction by introducing a lewis acid-base complex, tributylphosphine and triethylaluminum in dichloromethane.[18] Later in 2002 Taylor and co-workers applied these conditions to the synthesis of *epi*-epoxydon.[19] Leahy and Rafel observed unexpected rate acceleration in both amine and phosphine catalyzed MBH reactions upon lowering the reaction temperature to 0 °C (Scheme 1.10).[20] Typically MBH reactions take between 4-7 days to reach completion, but at 0 °C, the similar transformations were done in less than 12 hours. The authors rationalized this surprising observation by considering the transient enolate intermediates **A** and **B**, which are both in equilibrium with the starting material and react at different rates with the aldehyde. It was speculated that the relative concentration of **A** and **B** is different at 0 °C compared to at elevated temperature and thus the accelerated rate in MBH reaction reflects this difference. Evidence consistent with this proposal is that there was no rate enhancement in MBH reaction of acrylonitrile and benzaldehyde, since acrylonitrile is not predisposed to form intermediates like **A**.[21]

Fu and Netherton in 2001 addressed the air-sensitivity problem associated with trialkylphosphines by employing the air and moisture stable phosphonium salts as catalyst precursors and sodium phenoxide base (Scheme 1.11).[22] These conditions addressed both reaction efficiency and air sensitivity of the phosphine catalyst, the MBH product **1.56** is obtained in 94 % yield with a reaction time of only 1h.



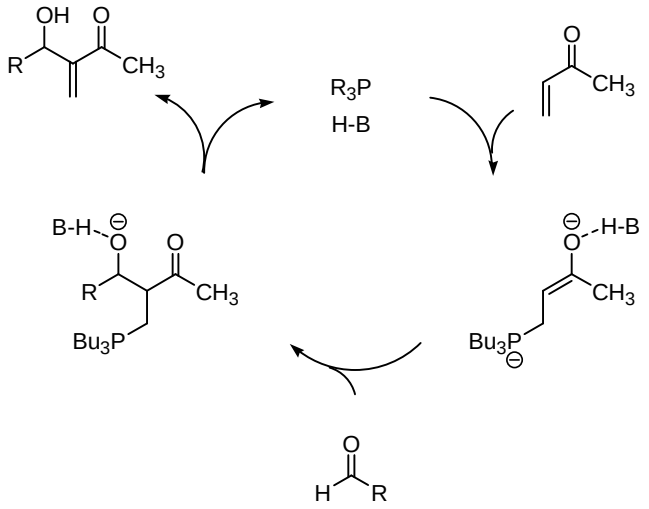
Scheme 1.10 Rate acceleration of MBH reaction at low temperature



Scheme 1.11 MBH reaction using phosphonium salts

The Morita-Baylis-Hillman reaction rate can be accelerated by using Lewis base-Brønsted acid co-catalysts.[23] According to mechanistic studies performed by Liu and Shi the Brønsted acid in the co-catalyzed systems stabilizes the phosphonium enolate intermediates *via* hydrogen-bonding with the enolate anion, thus driving the reaction

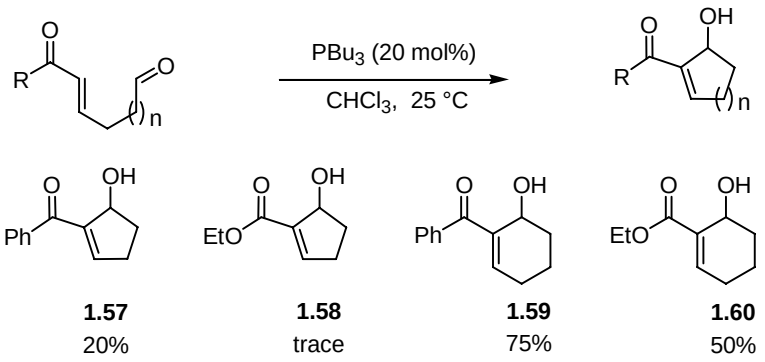
forward (Scheme 1.12).[23c] The co-catalyzed mechanism was investigated using ^{31}P NMR and ESI mass pectroscopy.



Scheme 1.12 A plausible mechanism for phosphine- Brønsted acid co-catalyzed MBH reaction

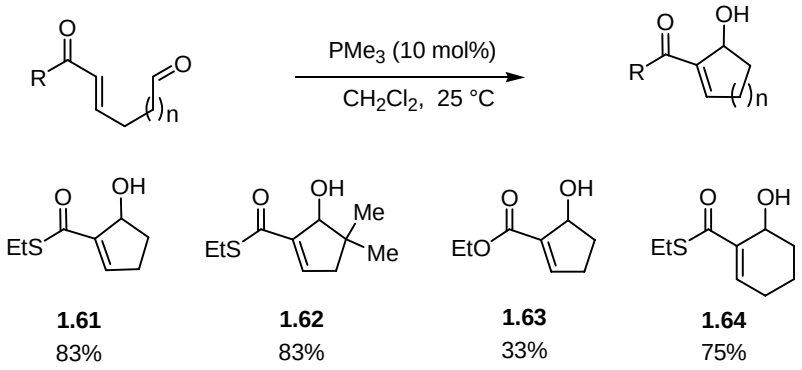
1.3.1 Intramolecular Morita-Baylis-Hillman Reaction

The first phosphine-catalyzed intramolecular variant of the Morita-Baylis-Hillman reaction was reported by Frater in 1992.[24] This reaction afforded cyclization products in low yields (17-23%). Murphy investigated this reaction further and reported cyclization of enones onto aldehydes to form both five and six- membered rings (Scheme 1.13).[25] Tributylphosphine catalyst gave good chemical yields for six-membered ring formation **1.59**, **1.60** and low yields for five-membered ring formation **1.57**, **1.58** (20% or less).



Scheme 1.13 Intramolecular Morita-Baylis-Hillman reaction

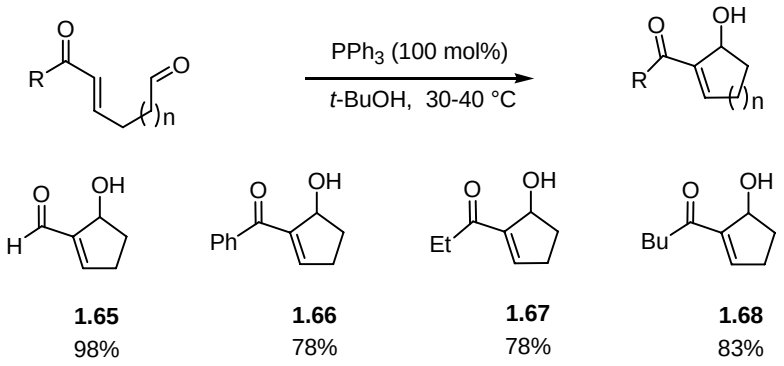
Keck and Welch observed that thioenoates cyclize efficiently onto aldehydes in the presence of trimethylphosphine to give both five-membered and six-membered ring products (Scheme 1.14).[26] The enoate cyclization onto the aldehyde was sluggish providing the MBH adduct **1.63** in low 33% yield. They found that enolizable aldehydes were more prone to side reactions, such as dimerization, and cylizations are more sensitive to slight variations in experimental conditions.



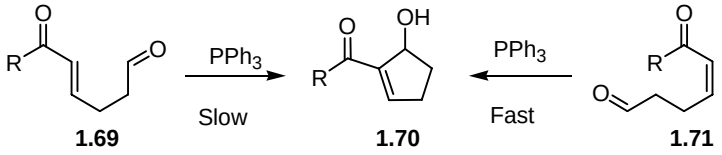
Scheme 1.14 Keck's intramolecular Morita-Baylis-Hillman reaction

In 2004 Koo and co-workers reported a triphenylphosphine mediated intramolecular MBH reaction (Scheme 1.15).[27] A dramatic solvent effect was observed in this reaction, when polar solvents like *t*-BuOH and MeCN provided excellent yields of

desired cyclic products while less polar solvents gave lower yields. Recently Toy and co-workers performed similar experiments using both *E* and *Z* enones with an appendant aldehyde (Scheme 1.16).[28] The substrates possessing (*Z*)-alkene stereochemistry **1.71** gave a higher yield of the desired cyclic product than did the corresponding *E* isomer **1.69**. This dramatic difference in reactivity was attributed to steric effects.



Scheme 1.15 Phosphine mediated intramolecular Morita-Baylis-Hillman reaction

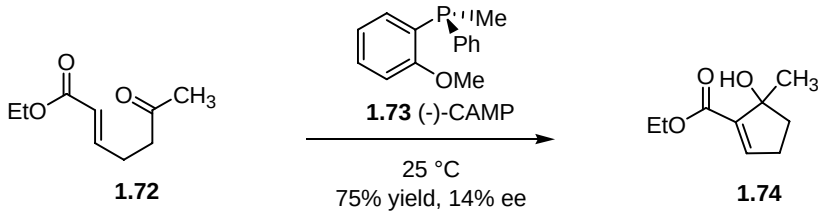


Scheme 1.16 Effect of alkene geometry on MBH reaction

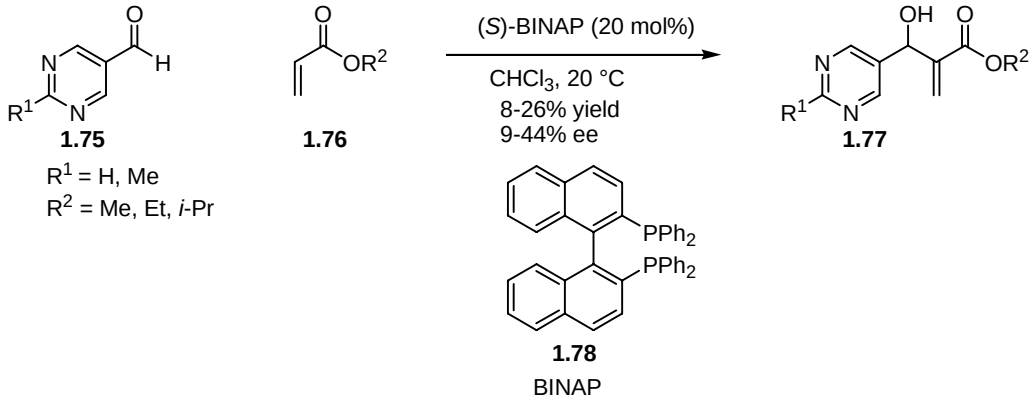
1.3.2 Asymmetric Morita-Baylis-Hillman Reaction

In 1992 Franter and co-workers reported the first asymmetric intramolecular MBH reaction using *p*-chiral phosphine (-)-CAMP **1.73** to catalyze cyclization of an enoate onto a ketone to afford cyclopenten-ol ester **1.74** in 14% ee (Scheme 1.17).[23, 29] Subsequent to this seminal result Soai in 1998 reported the first asymmetric

intermolecular MBH reaction utilizing chiral phosphine catalysts such as BINAP to catalyze the coupling of pyrimidine carboxaldehydes and methyl acrylate in low (9-44%) ee (Scheme 1.18).[30] They observed that the use of (*S*)-Tol-BINAP improved the chemical yield, however, the enantioselectivity was slightly decreased.



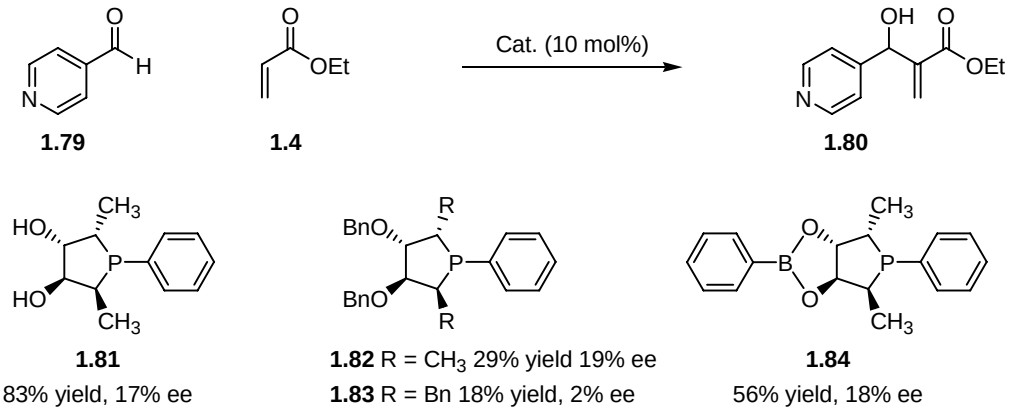
Scheme 1.17 Asymmetric intramolecular Morita-Baylis-Hillman reaction



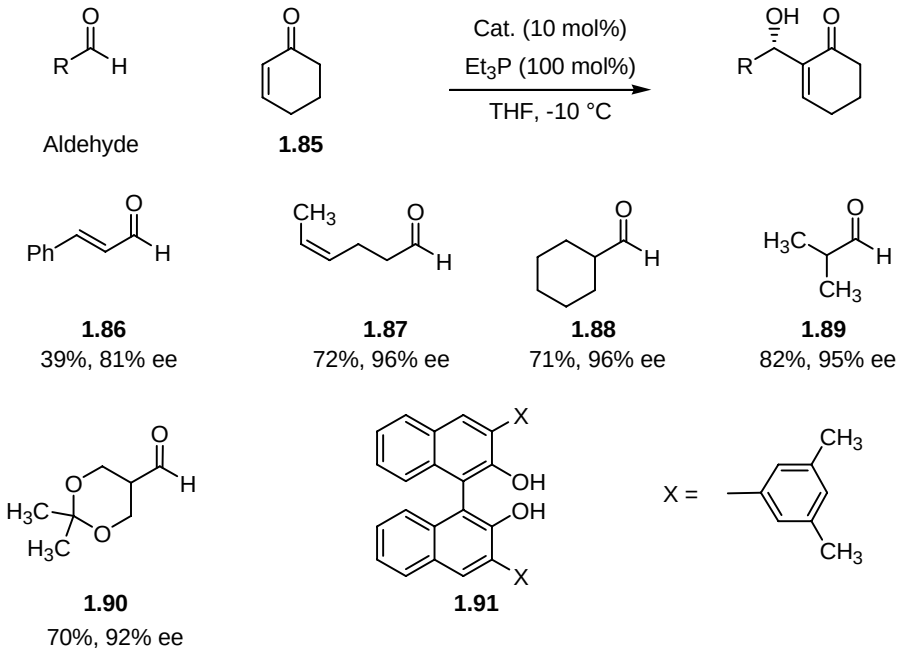
Scheme 1.18. The first phosphine-catalyzed asymmetric intermolecular MBH reaction

Zhang and co-workers prepared and applied D-manitol derived chiral phospholanes **1.81**-**1.84** to the asymmetric MBH reaction (Scheme 1.19).[31] These phosphine catalysts gave the MBH adduct **1.80** in low enantioselectivity. Rate enhancement was observed in the case of hydroxyl phospholane **1.81.** Ikegani reported in 2000, that phenol and BINOL (10 mol%) are effective bronsted acid co-catalysts when used with tributylphosphine (20 mol%) in the coupling of cyclic enones with aliphatic aldehyde to afford MBH adducts in almost quantitative yields.[23a] The reaction of 2-

cyclopentenone with hydrocinnamaldehyde in the presence of (*R*)-BINOL and tributylphosphine gave the desired MBH adduct in low ee (<10 ee) however, a calcium Lewis acid co-catalyst [Ca^{+2}-(*R*)-BINOL] (16 mol%) with tributylphosphine (10 mol%) gave the MBH adduct in 62% yield and 56% ee. Schaus and co-workers have developed a highly enantioselective MBH reaction using partially saturated BINOL derivatives substituted at the 3/3′ position as co-catalysts with triethylphosphine in the coupling of 2-cyclohexenone **85** and a variety of aldehydes (Scheme 1.20). [32] This reaction provides MBH adducts in good yields and excellent enantioseletivities (67-96% ee). Aliphatic aldehydes gave higher enantioselectivity than unsaturated or aromatic aldehydes.



Scheme 1.19 Zhang's asymmetric MBH reaction

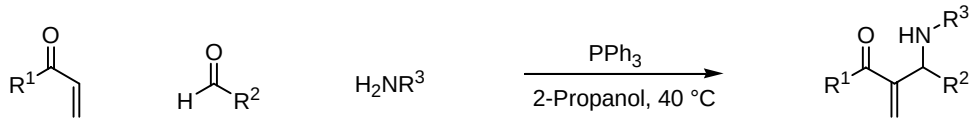


Scheme 1.20 MBH reaction catalyzed by BINOL derivative

Carretero and co-workers have shown that readily available ferrocenyldialkylphosphines are viable catalysts for MBH reaction between acrylates and aldehydes to provide MBH adducts in excellent yield (62-98%).[33] The asymmetric variant of this reaction was attempted using a set of planar chiral ferrocenyldialkylphosphines and the best enantioselectivities were obtained using Mandyphos as catalyst (up to 65% ee).

1.3.3 Aza-Morita-Baylis-Hillman-Reaction

A phosphine-catalyzed modification of the Morita-Baylis-Hillman reaction was first reported by Kahn and Bertenshaw in 1989 in which acrylates and aldehydes are coupled in presence of a sulphonamide or carbamate using triphenylphosphine to give 2-methylidene-3-amino esters (Scheme 1.21).[34] The α-aminoalkyl acrylates obtained in this reaction are precursors to β-amino acids.

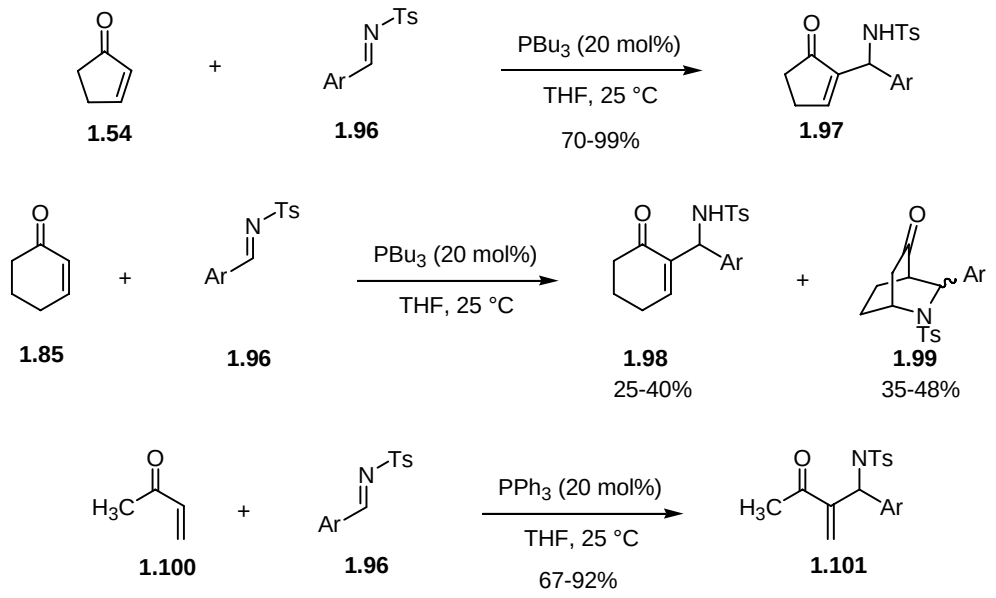


1.92 **1.93** **1.94** 50-98 % **1.95**

R^1 = Me, MeO
R^2 = Ph, *n*-Pr
R^3 = Ts, Boc, Cbz

Scheme 1.21 Phosphine-catalyzed aza-Baylis-Hillman reaction

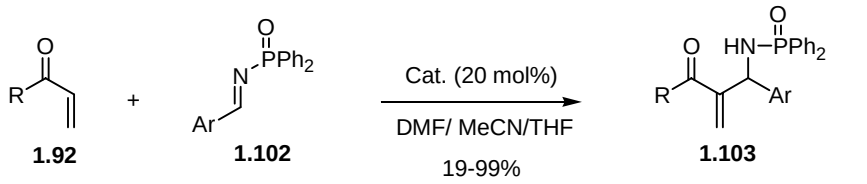
After the intial report by Kahn, Shi and co-workers have done extensive studies in aza-MBH reaction, where aldehydes have been replaced by the highly reactive *N*-arylidene-tosylamides, to give α-alkylidene-β-amino carbonyl compounds (Scheme 1.22).[35] 2-Cyclopentenone **1.54** and methyl vinyl ketone **1.100** participate in aza-MBH reaction in the presence of phosphine catalysts and a diverse range of activated imines derived from both electron rich and electron deficient aromatic aldehydes to give coupling products **1.97** and **1.101** in good yield. Phosphine catalysts are better catalysts than tertiary amines in this reaction. When a similar reaction was performed using 2-cyclohexenone **1.85**, a mixture of products was isolated: the MBH product **1.98** and two diastereomers of bicyclic products derived from the aldol reaction followed by intramolecular Michael addition of sulfonamide **1.99**. Recently Toy and co-workers have been able to perform aza-MBH reactions using polystyrene-supported triphenylphosphine as a catalyst for coupling methyl vinyl ketone and phenyl acrylate with various tosyl imines in good yields.[36]



Ar = neutral, electron-rich and electron-poor arenes

Scheme 1.22 Shi's aza-Morita-Baylis-Hillman reaction.

Subsequently, Shi and Zhao utilized *N*-arylidenediphenylphosphinamides **1.102** as electrophiles in aza-MBH reactions of a variety of acrylates, and acrylonitriles with methyl vinyl ketone using Ph_2PMe, PPh_3, and DABCO as catalysts (Scheme 1.23).[37] The reaction of *N*-arylidenediphenylphosphinamides **1.102** with methyl acrylates requires Ph_2PMe as a catalyst for optimal yields and for acylonitrile DABCO is the catalyst of choice. The authors report that the *N*-arylidenediphenylphosphinamides can be generated in situ by performing a one pot, three-component aza-MBH reaction of arylaldehydes, diphenylphosphinamide and methyl vinyl ketone in the presence of a Lewis acid $TiCl_4$ (0.8 equiv), PPh_3 (0.1 equiv) and Et_3N (12 equiv) to provide aza-MBH adducts in good yields. [35b]



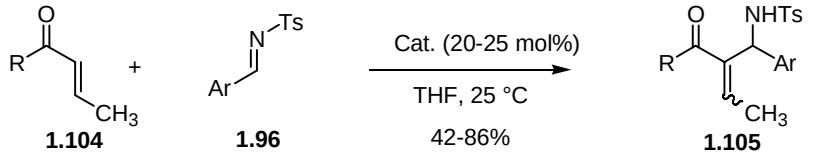
1.92 **1.102** **1.103**

R= Me, OMe
Ar = *p*-EtC_6H_4, *p*-$MeoC_6H_4$, *p*-FC_6H_4, *p*-ClC_6H_4,
Ar = *p*-BrC_6H_4, *p*-$NO_2C_6H_4$, C_6H_5-CH=CH

Cat. = PPh_3, Ph_2PMe, DABCO

Scheme 1.23 Enones and acrylates with *N*-arylidenediphenylphosphinamides in aza-MBH reaction

Shi and co-workers have studied a more challenging variant of the aza-Morita-Baylis-Hillman reaction, involving β-substituted activated alkenes and *N*-tosyl imines (Scheme 1.24).[38] In this reaction β-substituted aldehydes, enones, enoates, and thioenoates are coupled with a variety of *N*-tosyl imines **1.96** in THF at ambient temperature in the presence of a tertiary phosphine Lewis base such as PPh_2Me or $PPhMe_2$ to give the corresponding aza-MBH adducts in good yields as a mixture of *E*- and *Z*-stereoisomers.



1.104 **1.96** **1.105**

R = H, Ph, Me, OMe, OPh, SPh
Ar = *m*-$NO_2C_6H_4$, *p*-MeC_6H_4, *p*-FC_6H_4, *p*-ClC_6H_4,
p-BrC_6H_4, *p*-$NO_2C_6H_4$, *m*-F-C_6H_4

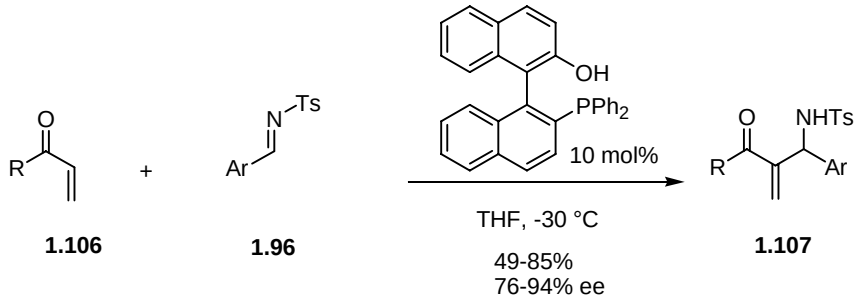
Cat. = $PhPMe_2$, Ph_2PMe,

Scheme 1.24 MBH reaction of β-substituted activated alkenes and electrophiles

1.3.4 Asymmetric aza-Morita-Baylis-Hillman Reaction

Following the successful discovery of the aza-Morita-Baylis-Hillman reaction of activated alkenes with *N*-tosyl imines in the presence of triphenylphosphine catalysts, Shi

and co-workers turned their attention to the asymmetric variant of this reaction using chiral triarylphosphine catalysts. They designed the 2′-diphenylphosphanyl-[1,1′]binaphthalenyl-2-ol catalyst, which catalyzes the asymmetric aza-MBH reaction of a diverse number of *N*-tosyl imines with methyl vinyl ketone or phenyl acrylate to give aza-MBH adducts in good yield with good enantioselectivity (76-94% ee (Scheme 1.25).[39] The reaction involving acrylates and acrolein was sluggish and thus required elevated temperatures of 40 °C in CH_2Cl_2 to give aza-MBH product in 52-77% ee. The authors believe that the chiral catalyst is bifunctional with the phosphine acting as a Lewis base and the phenolic OH acting as a Brønsted acid *via* hydrogen bonding. ^{31}P NMR spectroscopic data support an intramolecular hydrogen bonding between the phenolic OH and the carbonyl oxygen which in turn stabilizes the in situ generated enolate, resulting in a rigid transition state.



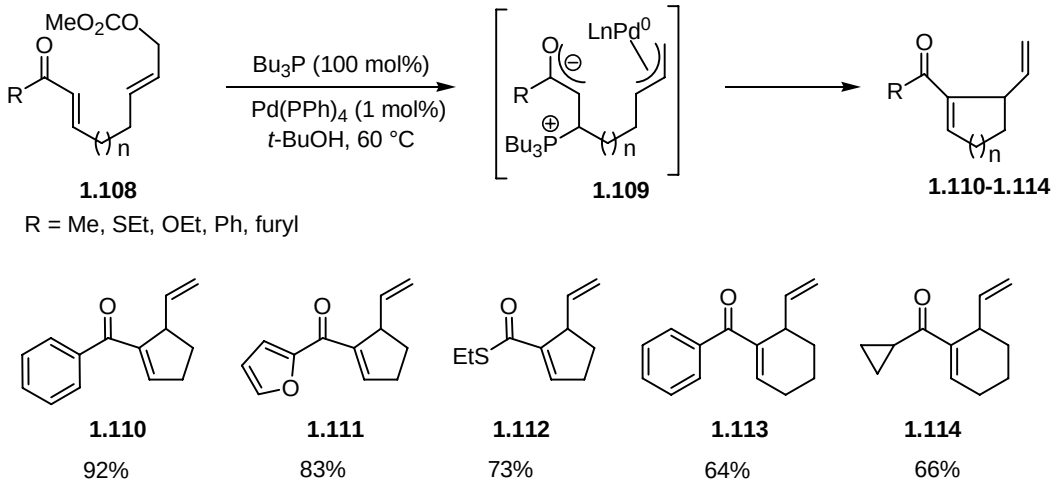
1.106 **1.96** **1.107**

R = H, Me, OPh
Ar = Ar = *m*-$NO_2C_6H_4$, *p*-MeC_6H_4, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$NO_2C_6H_4$, *m*-F-C_6H_4

Scheme 1.25 Asymmetric aza-MBH reaction

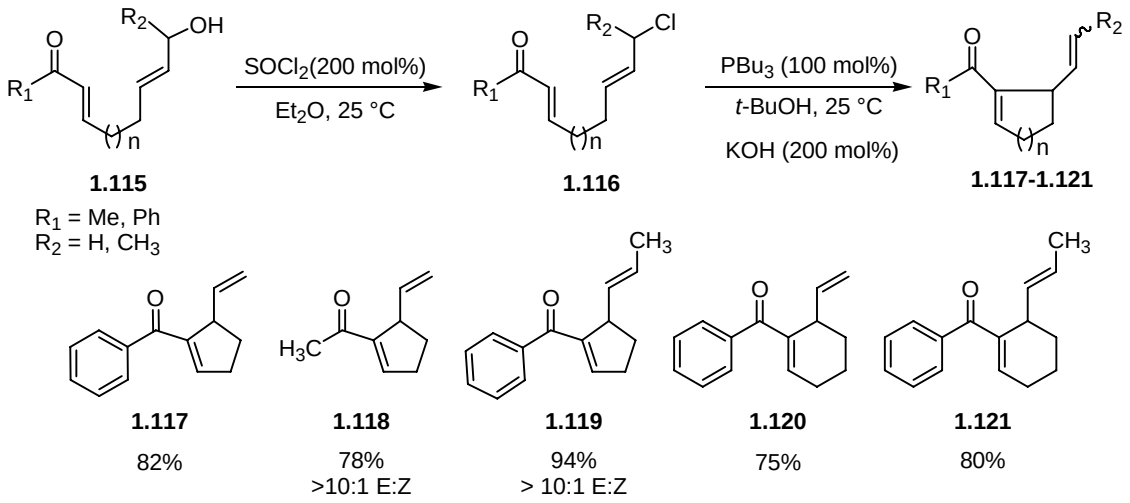
1.4 Phosphine-Catalyzed/Mediated α-Allylation of Enones

A variant of the Rauhut-Currier reaction that involves trapping of the transient enolates generated *via* phosphine conjugate addition to the enone with non-classical electrophiles such as π-allyls was reported by Krische and co-workers in 2003.[40] The authors utilized allylic carbonate as a latent electrophile, which is activated by a low valent palladium to form a palladium-π-allyl, at the same time an appendant enone is activated by tributylphosphine to generate a phosphium enolate intermediate **1.109** (Scheme 1.26). The two intermediates react to give a cyclic organophosphonium, which undergoes β-elimination to give the enone cycloallylation products **1.110-1.114**. This cycloallylation reaction provides five cyclic products **1.110-1.112** in good to excellent yields. The six-membered cycloallyation products **1.113-1.114** were obtained in slightly diminished yields. The authors observed that whereas enoates are not viable pronucleophiles, thioenoates **1.112** work well. This transformation is remarkable in that it merges both organic and transition metal catalysis by uniting nucleophilic features of the Morita-Baylis-Hillman reaction with the electrophillic features of the Trost-Tsuji reaction.



Scheme 1.26 Cycloallylation of enones using both phosphine and palladium catalysts

In 2005 Krafft and Haxell reported the first entirely organomediated intramolecular variant of Krische's cycloallylation reaction, where they utilized allylic chlorides as electrophillic partners (Scheme 1.27). [41] This transformation is a two step one-pot procedure for cycloallylation of enones that involves, conversion of the enone-allylic acohol substrate **1.115** to an allylic chloride **1.116** using thionyl chloride followed by addition of tributylphosphine catalyst to afford 5- and 6-membered ring cycloallylation products **1.117-1.121** in good yields. Both mono- and disubstituted alkenes are formed using this method with very good selectivity in the absence of transition metal catalysts, however exogenous stoichiometric base is required to facilitate the β-elimination step.



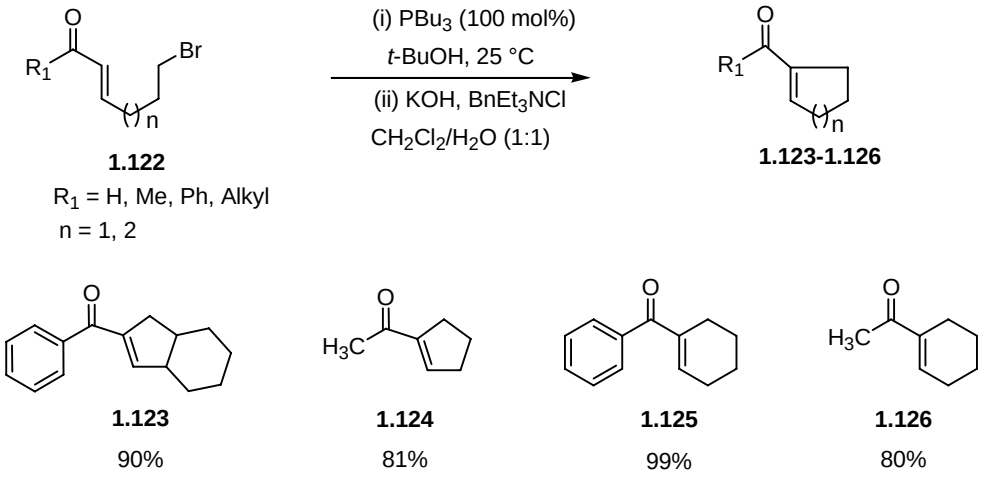
Scheme 1.27 Phosphine mediated cycloallylation of enones

1.5 Phosphine-Catalyzed/Mediated α-Alkylation of Enones

The classical Morita-Baylis-Hillman reaction (MBH) is an organocatalytic transformation that encompasses coupling of activated alkenes and sp^2 hybridized carbon electrophiles such as aldehydes, α-keto esters, 1,2-diketones, aldimines, enoates, enones and vinyl sulfones. Krafft and co-workers in 2005 reported the first organomediated variant of the intramolecular MBH reaction involving alkyl halides as electrophiles, to give the product of cycloalkylation (Scheme 1.28).[42] In this reaction cycloalkylation of enones is achieved in the presence of a stoichiometric amount of tributylphosphine in *t*-BuOH at ambient temperature followed by addition of aqueous base under phase transfer conditions, to afford both 5- and 6-membered ring products for example **1.123-1.126**. Remarkably, control experiments showed that tributylphosphine does not react with the alkyl halide to form the phosphonium salt.

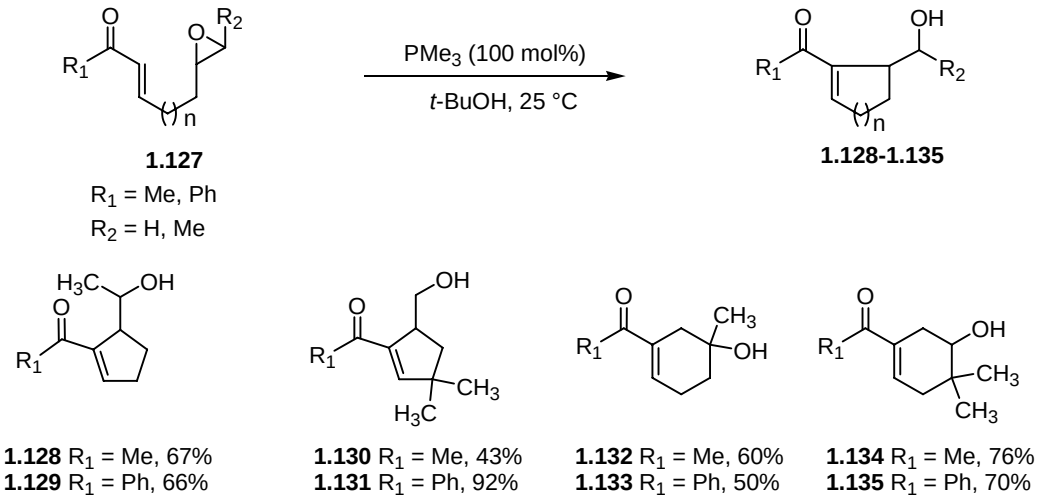
Having developed this synthetic method Krafft and co-worker turned their attention to rendering it catalytic in phosphine, this was achieved by lowering the PBu_3

catalyst loading to 20 mol% with minimal changes in reaction conditions.[43] Phosphine-catalyzed cycloalkylation of enones proceeds well to form both 5- and 6-membered cycloalkylation products in excellent yields. The authors observed that PBu_3 is the optimal catalyst for 5-membered ring formation and PMe_3 is the catalyst of choice for 6-membered ring formation.



Scheme 1.28 Phosphine-mediated cycloalkylation of enones

Recently Krafft and Wright reported the first phosphine mediated MBH reaction that utilizes epoxides as electrophiles (Scheme 1.29).[44] This unprecedented reaction that involves the use of epoxides in MBH reaction follows the usual mechanism where conjugate addition of PMe_3 to the enone gives rise to a Zwitterionic enolate that adds to the epoxide. Subsequent alkoxide induced elimination of the phosphine gives the cyclic homoaldol adducts **1.128-1.135**. For good selectivity between endo and exo cyclization onto the epoxide, substitution on the epoxide or the tether was necessary.

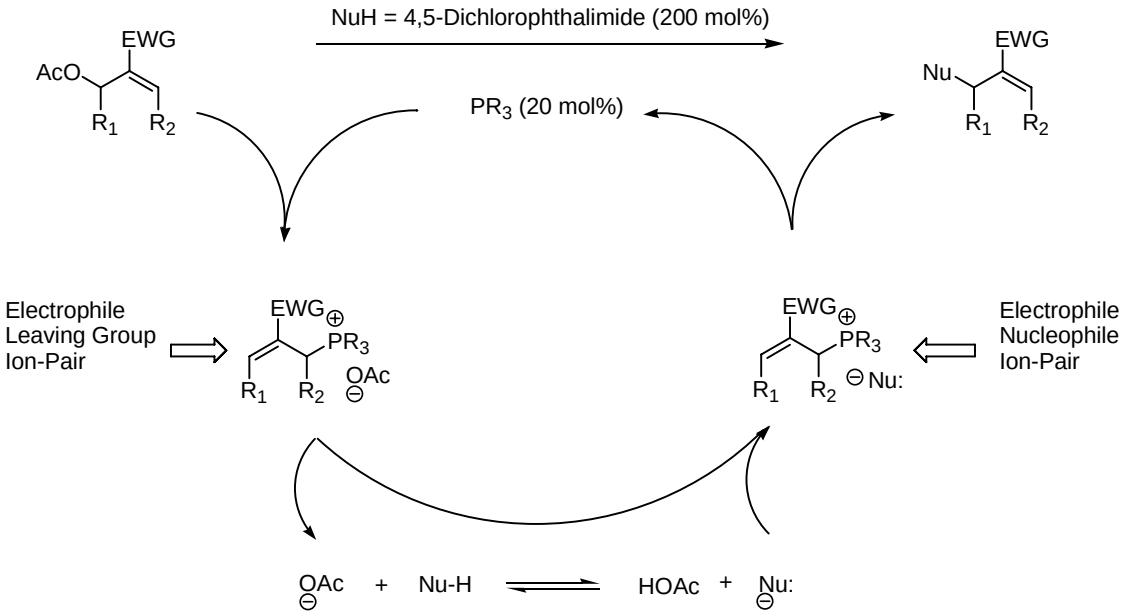


Scheme 1.29 Phosphine Mediated MBH reaction involving epoxide electrophiles

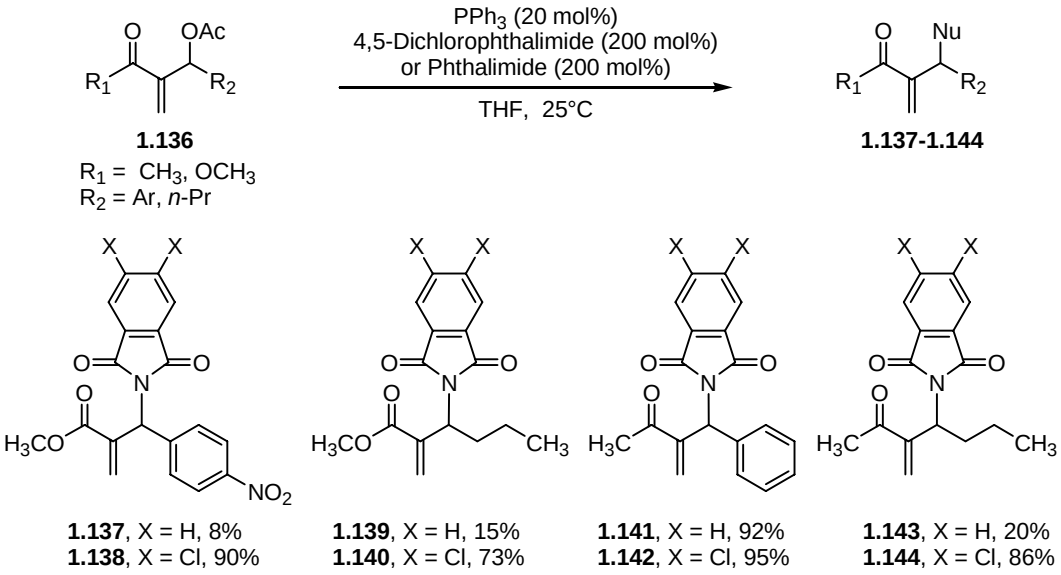
1.6 Phosphine Catalyzed Allylic Substution of MBH Acetates

In 2003 Krische and co-workers reported the first phosphine catalyzed reaction for allylic amination of MBH acetates.[45] The MBH acetates undergo regioselective allylic substitution in the presence of PPh_3 and 4,5-dichlorophthalimide or phthalimide through a tandem S_N2'- S_N2' substitution mechanism to give products of *N*-allylation (Scheme 1.30). By performing a survey of leaving group and pronucleophile combinations the authors observed a dramatic dependence on the Δ p*K*a between the conjugate acid of the leaving group and the pronucleophile vis-à-vis the generation of an electrophile-nucleophile ion pair. If the leaving group is not basic enough, deprotonation of the pronucleophile does not occur. Optimal yields were achieved using acetate as a leaving group and 4,5-dichlorophthalimide as a pronucleophile. The allylic amination products **1.138**, **1.140**, **1.142** and **1.144** were obtained in 73-95% (Scheme 1.31). Use of phthalimide as pronucleophile gave the allylic amination products **1.137**, **1.139** and **1.143** in low yields (18-20%). However, the reaction using methyl vinyl ketone derived MBH

acetate, which is a better electrophile was less sensitive to the nature of pronucleophile and provided an excellent yield (92%) of the phthalimide derived amination product **1.141**. All the products were obtained as single regioisomers presumably due to the generation of the electrophile-nucleophile ion pair that enhances regio-retention by suppressing direct addition of the nucleophile to the less substituted MBH acetate.



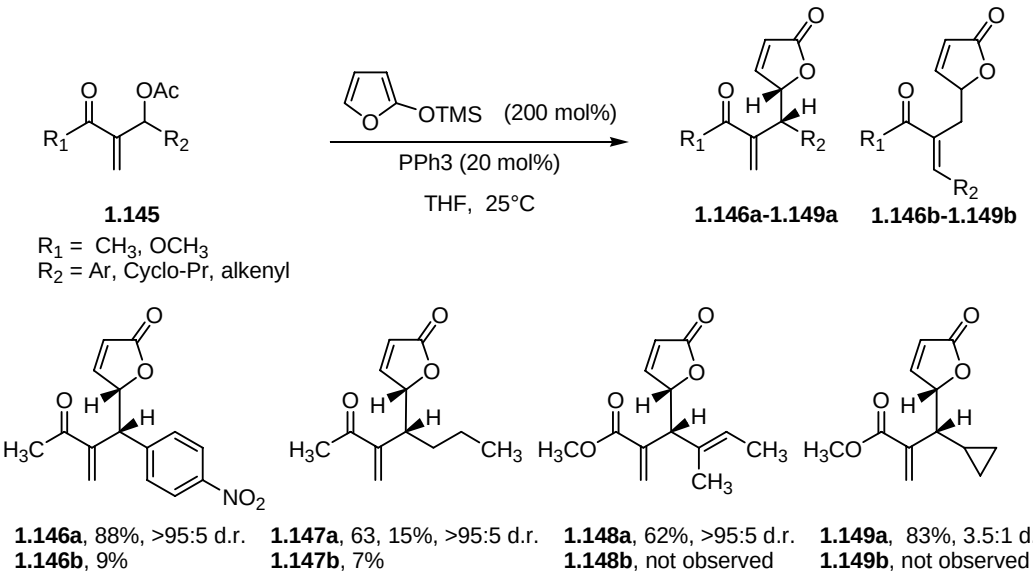
Scheme 1.30 A plausible mechanism for phosphine-catalyzed allylic amination



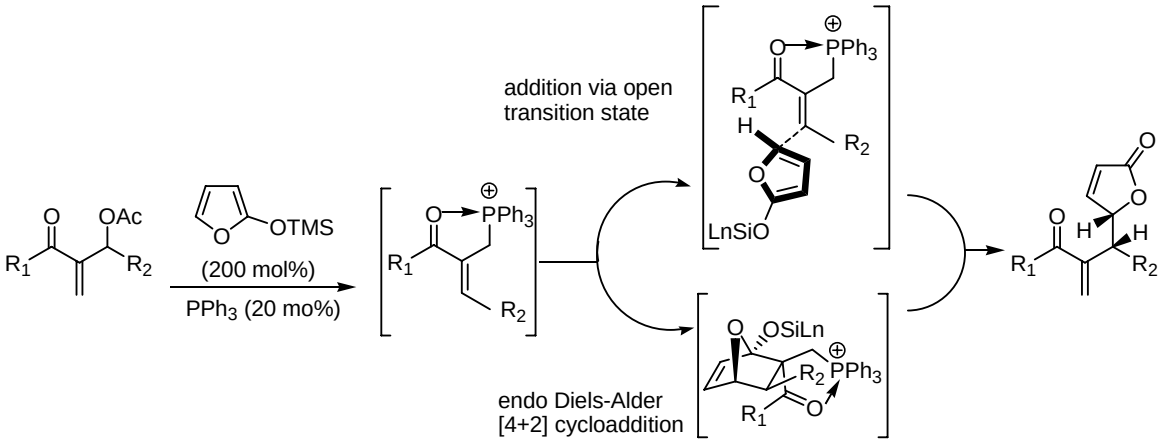
Scheme 1.31 Phosphine-catalyzed allylic amination of MBH acetates

The phosphine-catalyzed allylic substitution of MBH acetates was extended to carbon nucleophiles by Krische and Cho in 2005. [46] In the presence of 2-trimethylsilyloxy furan and a substoichiometric amounts of triphenylphosphine (20 mol%) MBH acetates **1.145** undergo regiospecific allylic substitution to afford the products of *C*-allylation **1.146-1.149** in good to excellent yields, along with good regio and diastereoselectivies (Scheme 1.32). The observed high diastereoselectivity in this reaction can be rationalized by invoking a closed transition state arising from an *endo*-selective Diels-Alder cycloaddition of the siloxyfuran ate complex with the enone resulting from conjugate addition of the phosphine to the MBH acetate followed by Grob-type fragmentation (Scheme 1.33). The observed high level of diastereoselectivity in the products **1.146-1.149** indicates that the intermediate phosphine adducts forms as a single enone geometrical isomer. The authors were able to control the absolute stereochemistry of this transformation by using a chiral auxiliary approach, where a (-)-8-

phenylmenthol ester was used in place of a methyl ester which provided excellent yield (87%) with control of the absolute stereochemistry.



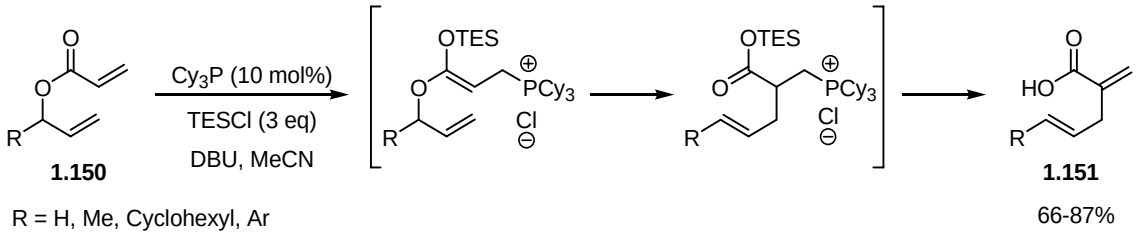
Scheme 1.32 Phosphine-catalyzed diastereoselective allylic substitution of MBH acetates



Scheme 1.33 A plausible mechanism for the phosphine-catalyzed allylic alkylation of MBH acetates

1.7 Other phosphine-Catalyzed Reactions Involving Activated Alkenes

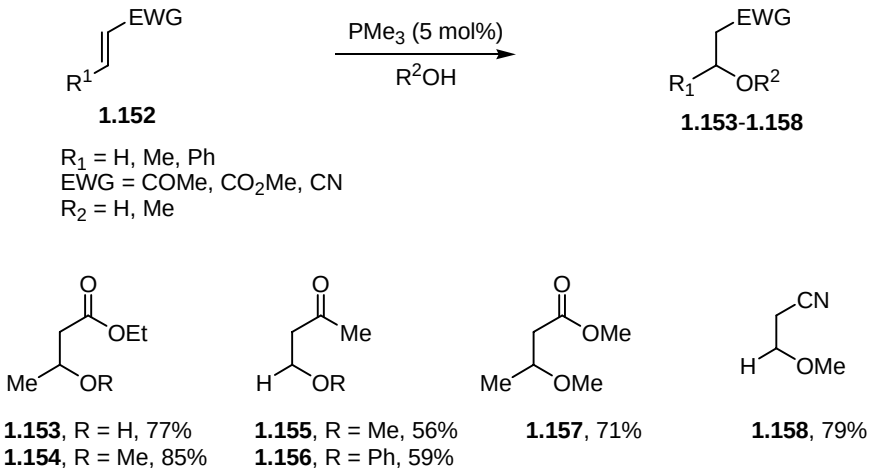
Evans and co-workers in 1978 reported a method for phosphonisilylation of α,β-unsaturated carbonyl compounds in the presence of triphenylphosphine and silylating agents.[47] Inanaga *et al* have employed this transformation to generate phosphonium silyl ketene acetals from allylic acrylates. The ketene acetal undergo Ireland-type [3,3] rearrangement and subsequent deprotonation by a base to provide the product **1.151** (Scheme 1.34).[48]



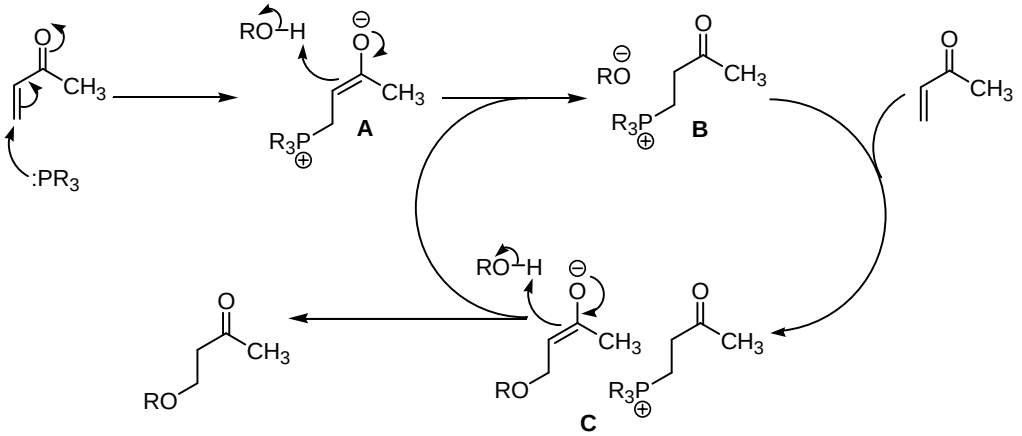
Scheme 1.34 Phosphine-catalyzed [3,3] rearrangement of allylic acrylates

Toste *et al* in 2003 reported a phosphine-catalyzed method for the hydration and hydroalkylation of enones, enoates and nitriles.[49] In this reaction addition of water and alcohols to acyclic enones, enoates, and nitriles in the presence of trimethylphosphine proceeds to provide hydration and hydroalkylation products **1.153**-**1.158** in good to excellent yields 56-95% (Scheme 1.35). Attempts to hydrate and hydroalkylate cyclic enones gave competitive dimerization products. It was also observed that whereas water, primary, secondary and aryl alcohols added to methyl vinyl ketone, tert-butyl alcohol did not. Based on these experiments, deuterium labeling, and ^{31}P NMR experiments the authors proposed a catalytic mechanism (Scheme 1.36). Conjugate addition of the phosphine to the methyl vinyl ketone forms the phosphonium enolate **A**, which

deprotonates an alcohol molecule forming an alkoxide phosphonium ion pair **B**. The alkoxide ion pair undergoes conjugate addition to another enone molecule resulting in enolate ion pair **C**. Subsequent protonation of the enolate in **C** gives the desired hydroalkylation product.



Scheme 1.35 Phosphine-catalyzed hydration and hydroalkylation of activated alkenes



Scheme 1.36 Proposed mechanism for hydration and hydroalkylation of activated alkenes

1.8 Summary and Outlook

In the phosphine-catalyzed cross Rauhut-Currier reaction the selectivity problem has been addressed *via* an intramolecular process. However, there are no enantioselective variants of this reaction reported in the chemical literature. The phosphine-catalyzed Morita-Baylis-Hillman reaction has been extensively studied in the last two decades. Asymmetric variants have been developed, however there are no highly enantioselective phosphine catalyzed intramolecular MBH reactions. For the asymmetric intermolecular MBH reaction high selectivity is only achieved using Lewis acidic co-catalysts such as BINOL derivatives. There is potential for design of phosphine catalysts that would confer high levels of asymmetry in both inter and intramolecular MBH reaction.

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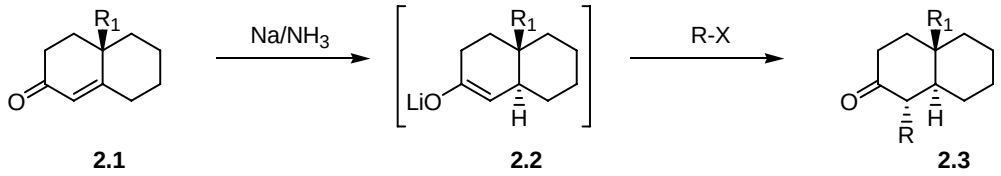
ENONES AND ENALS AS LATENT ENOLATES IN CATALYTIC C-C BOND FORMING PROCESSES: TOTAL SYNTHESIS OF (-)-PAROXETINE (PAXIL®)

Chapter 2: Catalytic α-Arylation of Enones, Enals, Nitroalkenes and the Total Synthesis of (-)-Paroxetine (PAXIL®)

2.1 Introduction

The Krische research group has an ongoing program predicated on the utilization of enones and enals as latent enolates. Enolate chemistry forms the cornerstone of numerous classical transformations in organic synthesis, including the aldol and Michael reactions.[1,2] Seminal studies by Stork demonstrate that tandem enone reduction-enolate alkylation is an effective method for regiospecific generation and trapping of the thermodynamically less stable enolate isomer **2.2** in the decalin system relating to steroid synthesis (Scheme 2.1).[3] The use of chemically robust enones as latent enolates is a promising alternative to the preformation of the more labile enols and enolates. Subsequent to Stork's report, catalytic methods for the activation of enones, which are suited for reaction with a variety of electrophiles have been developed. These methods are grouped in three categories: nucleophilic activation *via* conjugate reduction, nucleophilic activation *via* conjugate addition of carbon nucleophiles, i.e. carbometallative methods and nucleophilic activation *via* reversible conjugate addition of *N*- or *P*-nucleophiles i.e. nucleophilic organocatalysis. This chapter is devoted to work that encompass nucleophilic catalysis *via* conjugate addition of phosphine nucleophiles to enones, enals, nitroalkenes, and application of this method in total synthesis of (-)-paroxetine (PAXIL®).



Scheme 2.1 Regiospecific enolate generation *via* enone reduction

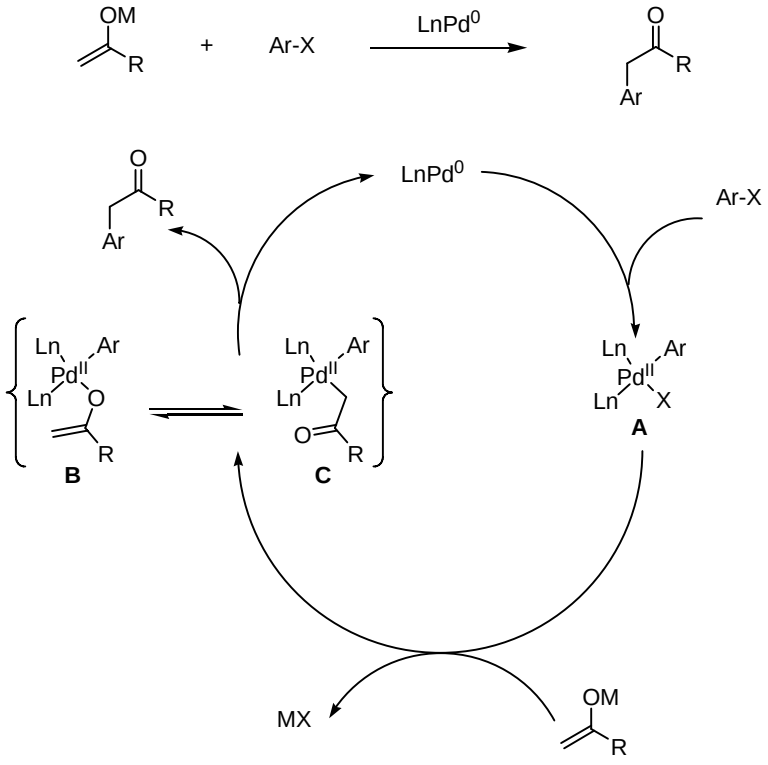
Nucleophilic catalysis represents an important sub-class of organocatalytic transformations.[4] We have developed a family of catalytic transformations in the area of phosphine catalysis, taking advantage of the unique reactivity of enolates generated *via* phosphine conjugate addition to α,β-unsaturated carbonyl compounds.[5] The phosphonium enolates obtained *via* phosphine conjugate addition to α,β-unsaturated carbonyl compounds have been trapped with classical electrophiles such as aldehydes, ketones and activated alkenes. Non-classical electrophiles like arenes are potential coupling partners for phosphonium enolates, though transition metal catalyzed enolate arylations are known, this would be the first account of an organocatalytic enolate arylation.

2.1.1 Transition Metal-Catalyzed Enolate Arylation

Enolate nucleophiles rarely react with aromatic or vinylic halides, even though numerous natural products, therapeutic agents, and synthetic intermediates posses an aromatic unit at the α-position of a carbonyl group. In 1973, Semmelhack and co-workers reported the first intramolecular nickel-catalyzed arylation of preformed ketone enolates.[6a] Subsequently, Millard and Rathke discovered an intermolecular variant involving nickel-catalyzed arylation and vinylation of preformed lithium enolates.[6b] In 1979, Fauvarque and Jutand reported a nickel and palladium-catalyzed arylation of the Reformatsky enolates.[6c] Palladium-catalyzed coupling of preformed tin enolates and enol

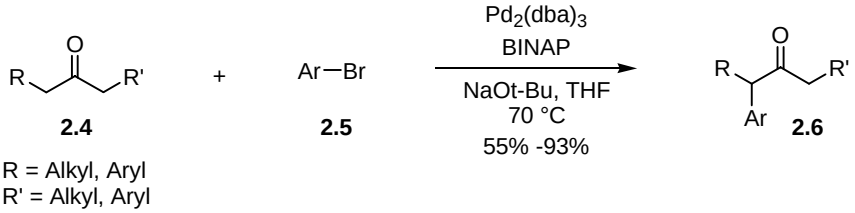
silanes were reported following Fauvarque's initial report.[7] These reactions are limited in substrate scope since they involve mainly acetates or methyl ketones. Ketone substrates possessing β-hydrogens gave product of β-ketone arylation. Another drawback to these methods is the requisite preformation of the enolate nucleophiles.

A plausible catalytic mechanism for the palladium catalyzed addition of enolates to aryl halides is shown in Scheme 2.2. It is believed that the reaction proceeds *via* oxidative addition of $LnPd^0$ to the aryl halide to afford the organometallic intermediate **A**. Transmetallation of the enolate nucleophile to Pd-complex **A** generates the organometallic intermediates **B** or **C**. Finally, reductive elimination from the intermediates **B** or **C** provides the arylation product and regenerates the $LnPd^0$ catalyst.



Scheme 2.2 A plausible mechanism for Pd-catalyzed ketone arylation

In 1997, Buchwald, Hartwig and Miura reported concurrently the first palladium-catalyzed reaction for direct coupling of ketones with arylbromides (Scheme 2.3).[8] This method requires a combination of $Pd_2(dba)_3$ and a phosphine ligand along with a stoichiometric amount of a strong base. The products of α-arylation of ketones are obtained in good to excellent yields; additionally this method is compatible with a wide variety of functional groups including ethers, nitriles, imines, amides and acetals.

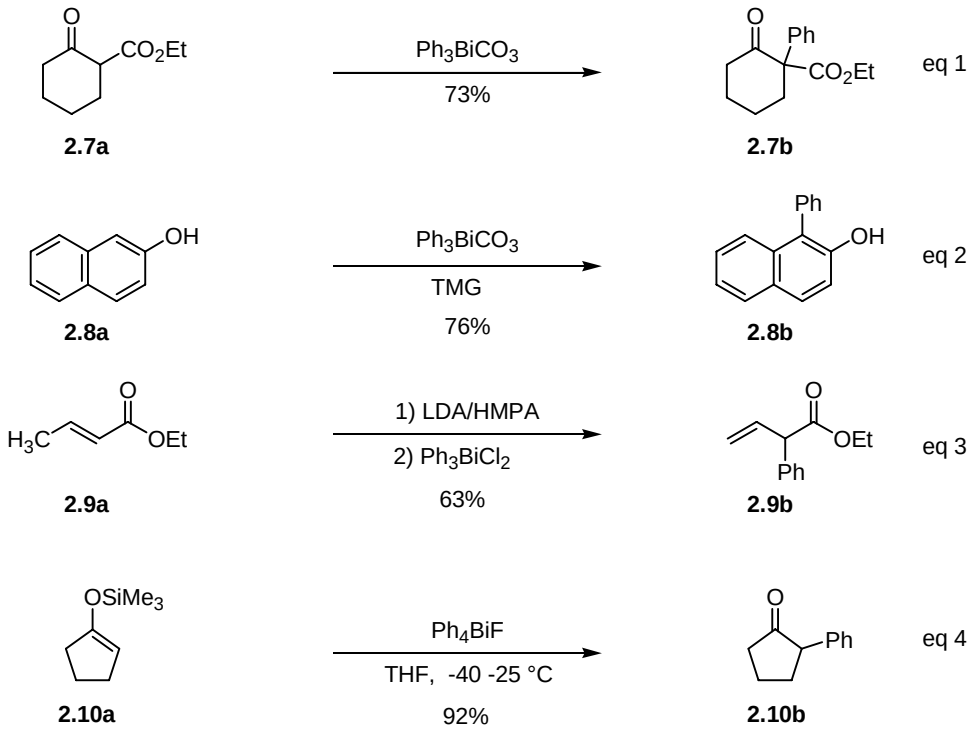


Scheme 2.3 Palladium-catalyzed direct α-arylation of ketones.

Buchwald and co-workers in 1998, reported the first catalytic asymmetric α-arylation of ketones using homochiral BINAP as a ligand for palladium to afford products with all-carbon quaternary centers.[9a] High chemical yields and enantioselectivity were achieved by using increased Pd catalyst loading (10-20 mol%). This is a major limitation to the synthetic utility of this reaction. This reaction was later improved by using only 2 mol% Pd catalyst loading and MOP-type ligands in the presence of NaO*t*-Bu at room temperature to afford aryl ketones in excellent yields.[9b] In 2001, Hartwig and Lee used optically active heterocyclic carbene ligands for an intramolecular palladium catalyzed amide arylation to afford α,α-disubstituted oxindole in modest enantioselectivity.[9c] Later Buchwald reported a highly enantioselective (83-98% ee) Ni(0)-catalyzed α-arylation of α-substituted γ–butyrolactones using chiral BINAP ligands with aryl chlorides and bromides.[9d]

2.1.2 Enolate Arylation Using Triarylbismuth(V) Reagents

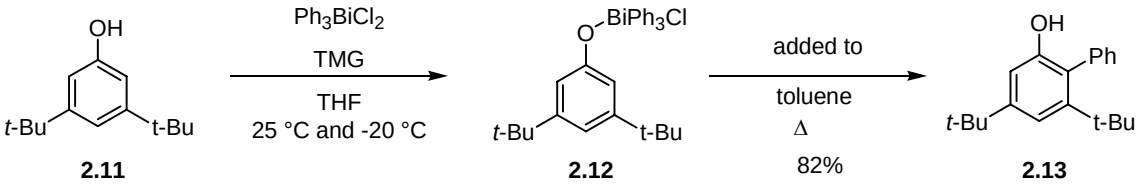
Seminal studies by Barton and co-workers involving oxidation of quinine to quininone resulted in α-arylated quininone product, this experiment revealed that bismuth(V) reagents[10] such as Ph_3BiCO_3 can be utilized as arylating agents.[11] Following this result a variety of enolizable substrates have been arylated using a diverse range of triarylbismuth(V) reagents (Scheme 2.4 eq 1).[12] Selective monoarylation is difficult to achieve in the case of 1,3–dicarbonyl compounds. Phenols can be *C*-arylated in the presence of triarylbismuth(V) reagents under both basic and neutral conditions (Scheme 2.4, eq 2).[13] Non-enolizable substrates could be arylated by first performing the enolates followed by treatment with triarylbismuth(V) reagents to provide products of α-arylation of carbonyl compounds (Scheme 2.4, eq 3 & 4).[14] Enolates trapped as enol silane can be readily arylated using tetraarylbismuth(V) fluoride reagents (Scheme 2.4, eq 4).



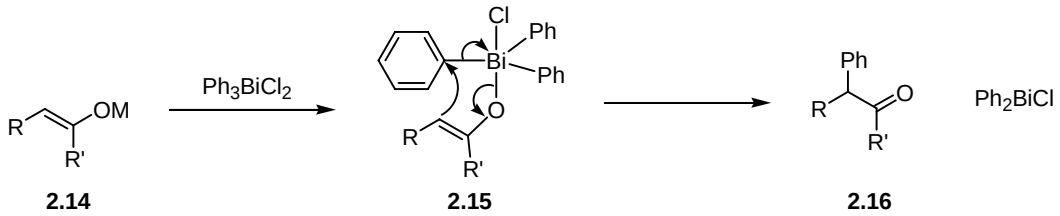
Scheme 2.4 Arylation of carbonyl compounds and phenols using bismuth(V) reagents

2.1.2.1 Mechanism for C-Arylation of Enolates Using Bismuth(V) Reagents

An intermediate containing a covalent Bi-O was invoked to explain the oxidation of alcohols by bismuth(V) reagents. A similar covalent Bi-O containing intermediate was proposed for *C*-arylation of phenols and enolates.[12b-c] The existence of the covalent Bi-O bond was corroborated by isolation and characterization of the (aryloxy)bismuth intermediate **2.12** from the reaction of the preformed anion of 3,5-di^{t}butylphenol **2.11** with tetramethylguanidine (TMG) and triphenylbismuth dichloride (Scheme 2.5).[13a] Careful thermal decomposition of intermediate **2.12** provided the *C*-phenylated phenol **2.13** in 82% yield. The second step of the arylation is a reductive elimination which is believed to proceed through a concerted mechanism, in which the π-electrons of the enol attack the ipso-carbon of the Ar-Bi bond, initiating phenyl migration **2.15** (Scheme 2.6).[15]



Scheme 2.5 Isolation and decomposition of intermediates

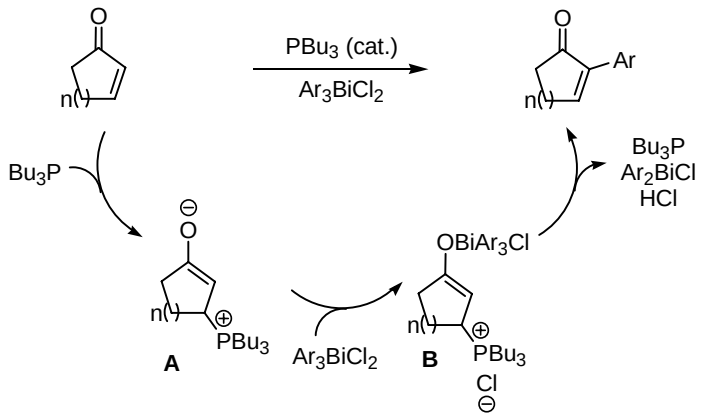


Scheme 2.6 Proposed mechanism reductive elimination step

2.2 Catalytic α-Arylation of Enones and Enals Using Triarylbismuth(V) Reagents

Transition metal-catalyzed enolate arylation[6-9] by way of ketone, ester, and amide pronucleophiles has received much attention however, general catalytic methods for arylation of enones have not been described.[16] We have developed a method for regiospecific α-arylation of enones and enals under conditions of nucleophilic catalysis.[17] Cyclic enones and enals can be arylated upon exposure to 1 equivalent of Ar_3BiCl_2 and Hünig's base in the presence of a catalytic amount of tributylphosphine to afford α–aryl enones and α–aryl enals in good to excellent yields.

A catalytic mechanism for this transformation is envisioned based on the mechanistic studies by Barton and co-workers for arylation of alkali enolates (Scheme 2.7).[13a] Conjugate addition of tributylphosphine to the enone generates phosphonium enolate **A**, which then adds to triarylbismuth(V) dichloride reagent to provide intermediate **B**. Reductive elimination followed by β-elimination of tributylphosphine affords the α-aryl enone. The feasibility of this phosphine-catalyzed enone α–arylation using triarybismuth(V) reagents requires the compatibility of the Lewis basic tributylphosphine and the Lewis acidic bismuth(V) reagent. Bismuth(V) reagents are good oxidants, however we believe that oxidation of the bulky tributylphosphine should be slower than aryl transfer.



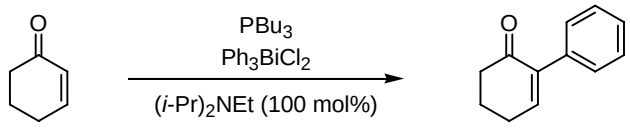
Scheme 2.7 Proposed catalytic mechanism for α–arylation of enones and enals

2.2.1 Optimization

To test the feasibility of this phosphine-catalyzed α–arylation of enones, 2-cyclohexenone **2.17a** (100 mol%) was exposed to Ph_3BiCl_2 (100 mol%) in the presence of tributylphosphine (100 mol%) and Hünig's base (100 mol%) at room temperature in CH_2Cl_2 (1M) solvent. Gratifyingly, the product of α-arylation **2.17b** was obtained in 87% isolated yield as a single regioisomer as determined by ^{1}H NMR analysis (Table 2.1, entry 1). Upon decreasing the catalyst loading to 20 mol%, α-arylation product was obtained in 85% yield, however the reaction time increased to 42 hours (Table 2.1, entry 2). With the knowledge that *t*-BuOH as a solvent enhances the rate in the Morita-Baylis-Hillman reaction, it was speculated that *t*-BuOH might be a good solvent for this reaction, however attempts to run the reaction in this solvent gave a modest 67% yield of the desired product (Table 2.1, entry 4). This low yield could be attributed to the poor solubility of triphenylbismuth dichloride in *t*-BuOH. Finally, using a mixed solvent system of CH_2Cl_2 and *t*-BuOH (9:1) gave the α-arylation product **2.17b** in 93% yield

with a significant decrease in reaction time (Table 2.1, entry 5). These conditions served as the standard condition for this transformation.

Table 2.1 Optimization table for α-arylation of enones



2.17a **2.17b**

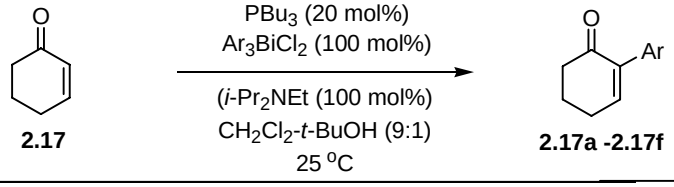
Entry	Ph_3BiCl_2 (mol%)	PBu_3 (mol%)	Solvent (1M)	Time (hr)	Temp (°C)	Yield (%)
1	100	100	CH_2Cl_2	26	25	87
2	100	20	CH_2Cl_2	42	25	85
3	100	20	EtOAc	36	25	48
4	100	20	*t*-BuOH	24	40	67
5	**100**	**20**	**CH_2Cl_2/*t*-BuOH (9:1)**	**13**	**25**	**93**

2.2.2 Substrate Scope

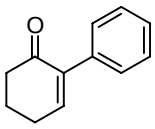
To probe the substrate scope of this transformation, a variety of triarylbismuth(V) dichlorides were prepared by treating ArMgBr with $BiCl_3$ followed by oxidation of the resulting triarylbismuth(III) compounds with chlorine gas or sulfuryl chloride (SO_2Cl_2).[18] Under our standard conditions, the catalytic α-arylation of 2-cyclohexenone **2.17** (Table 2.2) and 2-cyclopentenone **2.18** (Table 2.3) were performed. The formation of α-arylation products **2.17b-2.17e** and **2.18b-2.18e** demonstrates that transfer of aryl groups from *para*-substituted triarylbismuth dichlorides proceeds readily and in good yields (Tables 2.2 and 2.3). The ability to transfer bromo-substituted arenes illustrates the functional group tolerance of this methodology compared to nickel or palladium-catalyzed enolate arylation methods. The formation of α-arylation products **2.17f-2.17h**

and **2.18f-2.18h** shows that *meta*-substituted aryl groups transfer efficiently, even in the case of the electron rich methoxy-substituted systems. Unfortunately, *para*-methoxyarenes gave trace amount of product. This could be attributed to the strong π-donating effect of the methoxy moiety, which reduces the Lewis acidity of the triarylbismuth dichoride. Transfer of disubstituted arenes is achieved effectively as demonstrated by the formation of α-arylation products **2.17i** and **2.18i.**

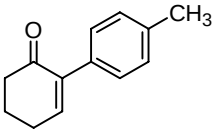
Table 2.2. Phosphine-catalyzed α-arylation of 2-cyclohexenone using Ar_3BiCl_2 reagents



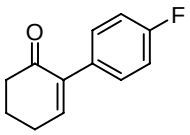
2.17 **2.17a -2.17f**



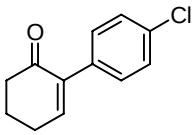
2.17a, 93%



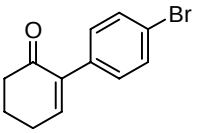
2.17b, 44%



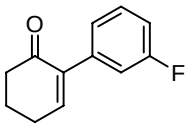
2.17c, 66%



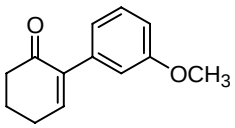
2.17d, 80%



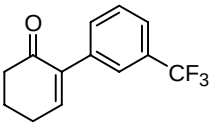
2.17e, 71%



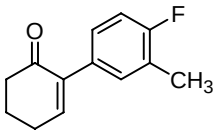
2.17f, 76%



2.17g, 67%

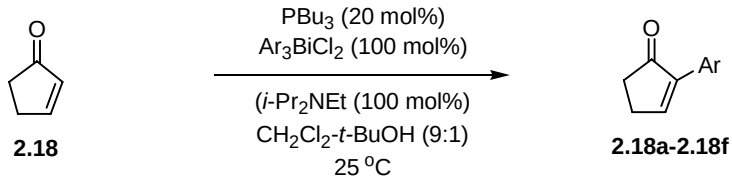


2.17h, 65%

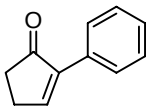


2.17i, 75%

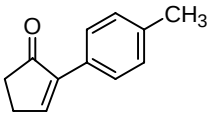
Table 2.3. Phosphine-catalyzed α-arylation of 2-cyclopetenone using Ar_3BiCl_2 reagents



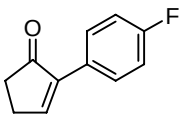
2.18 → **2.18a-2.18f**



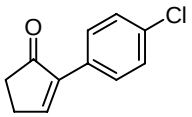
2.18a, 70%



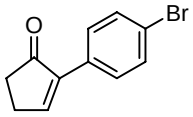
2.18b, 62%



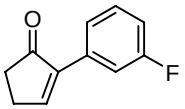
2.18c, 79%



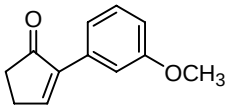
2.18d, 75%



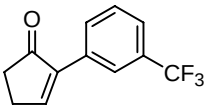
2.18e, 80%



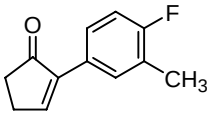
2.18f, 73%



2.18g, 85%



2.18h, 72%

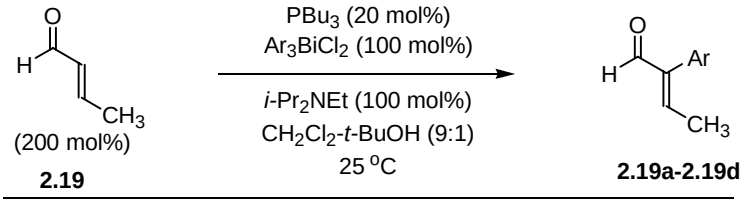


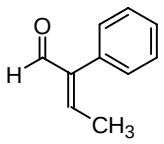
2.18i, 89%

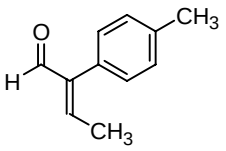
To further explore the substrate scope of this transformation, we screened a variety of acyclic enones. Experiments revealed that α,β-unsaturated pronucleophiles need substitution at the β-position to attenuate competitive anionic polymerization. Attempts to α-arylate acylic enones gave trace amount of the desired product, leading to the speculation that reactive pronucleophiles must achieve an *s-trans* conformation. For example cyclic enones such as 2-cyclohexenone and 2-cyclopentenone which are reactive pronucleophiles are locked in the *s-trans* conformation. To test our hypothesis, we examined the α-arylation of β-substituted enals such as crotonaldehyde which exist predominantly in the *s-trans*-conformation. Gratifyingly, crotonaldehyde **2.19** participates in the α-arylation to provide α-arylated enals **2.19a-2.19d** in modest to good

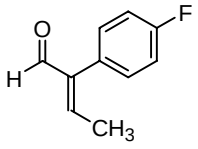
yields (Table 2.4) under standard conditions though two equivalents of crotonaldehyde must be employed. The stereochemical assignment was based on ^{1}H NMR of previously reported material for **2.19a**,[53] the diagnostic vinylic proton was observed at 6.7 ppm as reported in literature for the *E*-isomer.

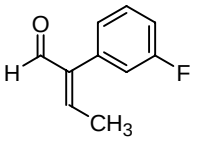
Table 2. 4**.** Phosphine-catalyzed α-arylation of crotonaldeyde using Ar_3BiCl_2 reagents




2.19a, 61%


2.19b, 49%


2.19c, 70%


2.19d, 54%

2.3 Catalytic α-Arylation of Nitroalkenes Using Triarylbismuth(V) Reagents

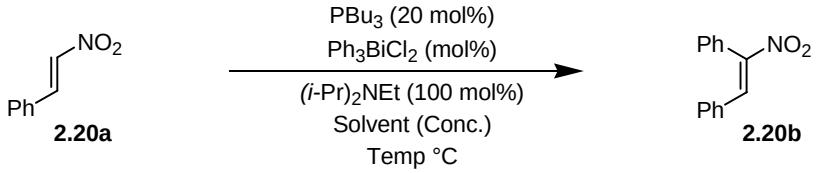
The α,β-unsaturated nitroalkenes are useful and versatile synthetic intermediates in organic chemistry.[19] The electron deficient nature of nitroalkenes facilitates their application in the Diels-Alder reaction as dienophiles[20] and in conjugate addition chemistry as Michael acceptors.[21] In addition to these applications, the nitro group can be easily converted to a variety of functional groups including aldehydes, ketones, oximes, nitrones, hydroxylamines, and amines.[19b-c, 22] Historically, nitroalkenes are known for their biological activity as insectides,[23] fungicides,[24] antibacterials,[25] and antitumor agents.[26] Inspired by the versatility and the biological importance of nitroalkenes, we focused our attention to the arylation of nitroalkenes in an effort to extend the scope of our phosphine-catalyzed regiospecific α-arylation methodology.[17]

2.3.1 Optimization

To assess the feasibility of utilizing nitroalkenes, as pronucleophiles, β-nitrostyrene **2.20a** (100 mol%) was exposed to Ph_3BiCl_2 (110 mol%) and Hünig's base (100 mol%) in the presence of tributylphosphine (20 mol%) at room temperature in THF. Gratifyingly, the α-arylation product **2.20b** was obtained in 50% isolated yield as a single alkene isomer, as determined by ^{1}H NMR analysis, where the vinylic proton is observed at 8.23 ppm for the *E*-isomer and literature reports 8.25ppm.[59a] and melting point 72-73 °C, Lit[59b] is 74 °C (Table 2.5, Entry 1). Under otherwise identical conditions, but doubling the loading of Ph_3BiCl_2 led to an increase in yield of **2.20b** to 56% (Table 2.5, Entry 2). Upon changing the solvent to EtOAc, **2.20b** was obtained in 14%, isolated yield

(Table 2.5, Entry 3). This is attributed to the poor solubility of Ph_3BiCl_2 in EtOAc. Performing the reaction at 50 °C improved the solubility of Ph_3BiCl_2, resulting in a 67% yield of **2.20b** with a significant shortening of the reaction time. (Table 2.5, Entry 4). Efforts to further optimize this reaction by varying concentration and reaction temperature did not result in any improvement in chemical yield (Table 2.5, Entries 5-7). These reaction conditions represent our standard conditions for α-arylation of nitroalkenes (Table 2.5, entry 4).

Table 2.5 Optimization table for α-arylation of Nitroalkenes



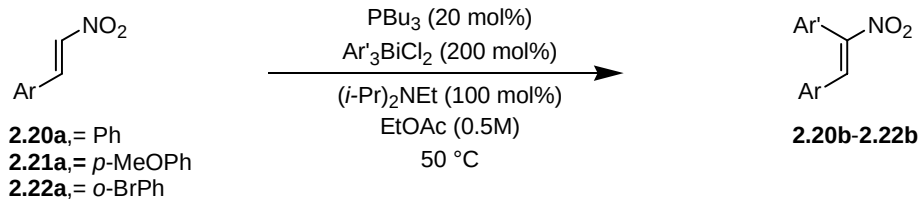
Entry	Solvent (Conc.)	Ph_3BiCl_2 (mol%)	Temp °C	Time (h)	%Yield
1	THF (0.5M)	110	25	36	50
2	THF (0.5M)	200	25	42	56
3	EtOAc (0.5M)	200	25	48	14
4	**EtOAc (0.5M)**	**200**	**50**	**3**	**67**
5	EtOAc (1M)	200	50	2	65
6	EtOAc (0.2M)	200	50	12	65
7	EtOAc (0.5M)	200	70	2	62

2.3.2 Substrate Scope

Under our standard conditions, the catalytic α-arylation of aromatic nitroalkenes was explored using diverse triarylbismuth(V) dichlorides. β-Nitrostyrene **2.20a** undergoes α-arylation readily to provide products **2.20b-2.20e** in good yield (Table 2.6). As demonstrated by the formation of α-arylation products **2.20c-2.20e** para, meta and

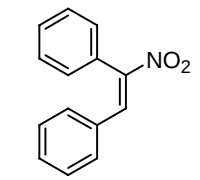
disubstituted triarylbismuth(V) dichlorides transfer aryl groups efficiently, even when the α,β-unsaturated pronucleophile bears an electron rich methoxy- and methyl substituents. The α-arylation of *p*-methoxy-β-nitrostyrene **2.21a** proceeds efficiently to provide products **2.21b-2.21d** in good yields and as single alkene isomer (Table 2.6). As shown by product **2.22b** *o*-bromo-β-nitrostyrene **2.22a** undergoes α-arylation effectively. Notable is the transfer of the bromo substituted aryl group as illustrated by formation of **2.21b**, which would be problematic under the conditions of palladium catalysis.

Table 2.6 Phosphine catalyzed α-arylation of aromatic nitroalkenes using triarylbismuth(V) reagents.

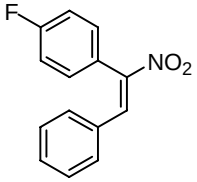


2.20a,= Ph
2.21a,= *p*-MeOPh
2.22a,= *o*-BrPh

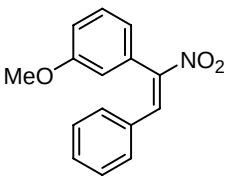
2.20b-**2.22b**



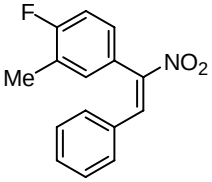
2.20b, 67%



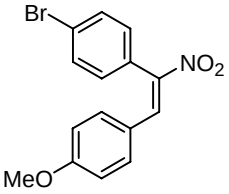
2.20c, 74%



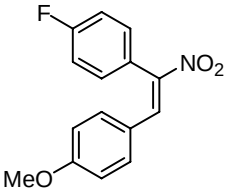
2.20d, 68%



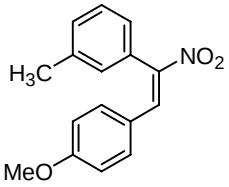
2.20e, 64%



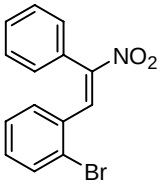
2.21b, 61%



2.21c, 76%



2.21d, 69%

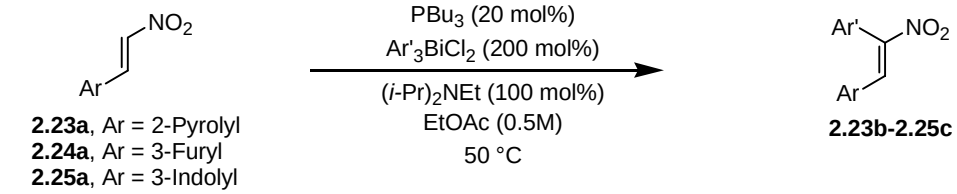


2.22b, 63%

. To further probe the scope of this transformation we synthesized heteroaromatic nitroalkenes containing furyl, indolyl, and pyrolyl moieties, *via* Henry reaction using the

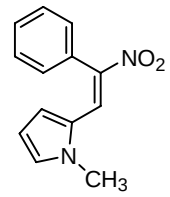
corresponding aldehydes and nitromethane. Arylation of these heteroaromatic nitroalkenes **2.23a-2.25a** proceed effectively to provide products of α-arylation **2.23b-2.25c** in good yields as a single alkene isomer as determined by ^{1}H NMR analysis (Table 2.7).

Table 2.7 Phosphine catalyzed α-arylation of hetero-aromatic nitroalkenes using triarylbismuth(V) reagents.

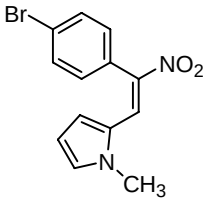


2.23a, Ar = 2-Pyrolyl
2.24a, Ar = 3-Furyl
2.25a, Ar = 3-Indolyl

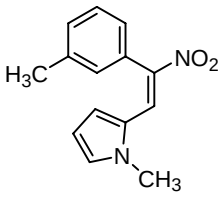
2.23b-2.25c



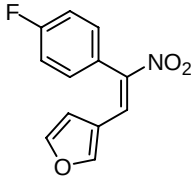
2.23b, 78%



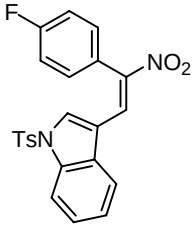
2.23c, 67%



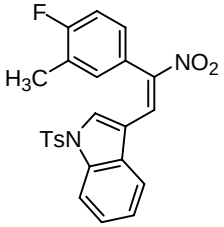
2.23d, 51%



2.24b, 72%



2.25b, 69%



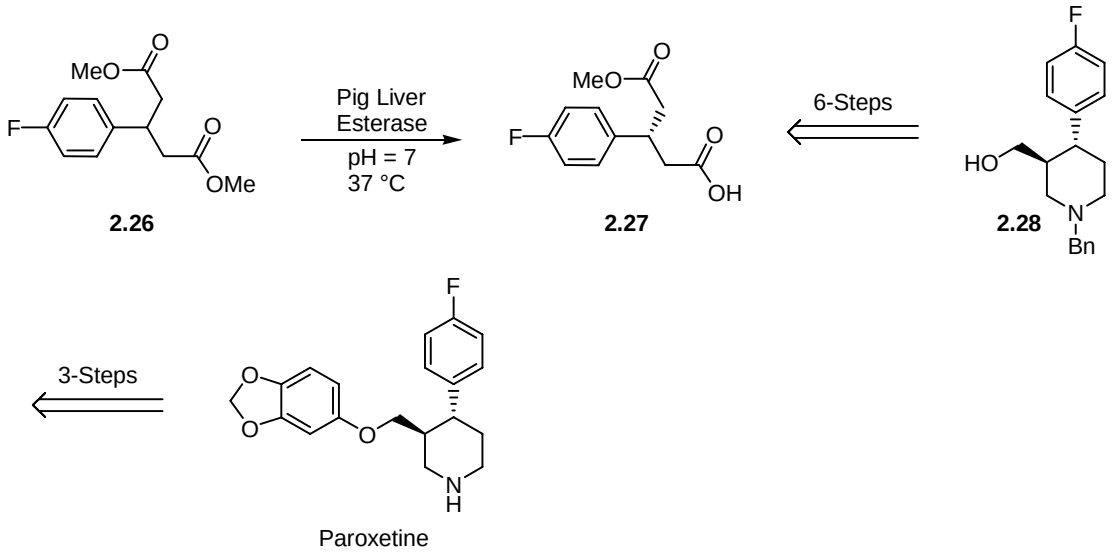
2.25c, 74%

2.4 Application of the Phosphine-Catalyzed Enone α-Arylation in Formal and Enantioselective Total Synthesis of Paroxetine (PAXIL®)

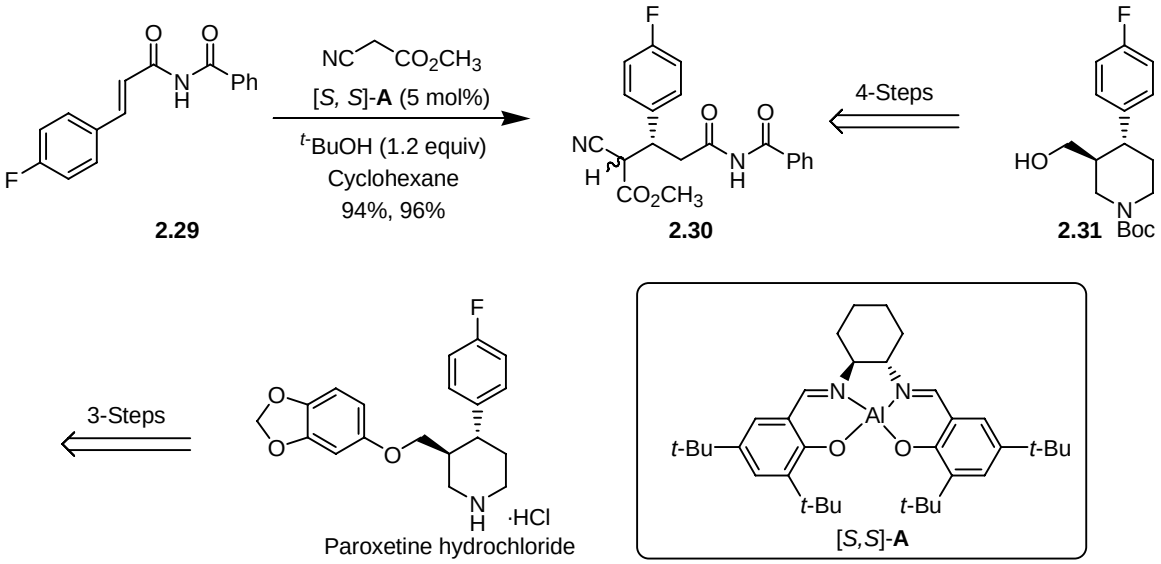
In the previous sections we described the development of a catalytic method for the regiospecific α-arylation of enones, enals, and nitroalkenes wherein transiently generated (β-phosphino)enolates or oxaphospholenes are captured by arylbismuth(V) reagents. The scope of this process complements the corresponding palladium catalyzed enolate arylations, as strongly basic reagents are not required for enolate generation and the use of enones as enolate precursors enables regiospecific enolate generation.[8,9] Here, the synthetic utility of the phosphine-catalyzed enone α-arylation is highlighted through its strategic use in a concise formal and enantioselective total syntheses of the blockbuster antidepressant (-)-paroxetine (PAXIL).

Paroxetine, a GlaxoSmithKline product marketed as Paxil/Seroxat, is an enantiomerically enriched *trans*-3,4-disubsituted piperidine used for the treatment of depression, obsessive compulsive disorder, and panic disorder.[27] As one of the leading prescription drugs worldwide, paroxetine has received considerable attention from synthetic chemists, evoking a surprisingly diverse array of strategies for its asymmetric synthesis. To date, approaches to the asymmetric synthesis of paroxetine encompass the physical resolution of racemates,[28] enzyme catalyzed asymmetric transformations,[29] chiral auxiliary based approaches,[30] asymmetric deprotonation using chiral bases,[31] catalytic enantioselective transformations,[32] as well as the use of naturally occurring chiral starting materials.[33]

Due to the large number of reported prior synthesis of PAXIL, we will discuss the GlaxoSmithKline synthesis[29c,e] (Scheme 2.8) and the shortest enantioselective synthesis reported by Jacobsen group.[32] The GlaxoSmithKline synthesis is 13 linear steps featuring an enzymatic resolution of the prochiral diester **2.26** to provide intermediate **2.27**. This intermediate has been elaborated to amino alcohol **2.28** in 6 steps and **2.28** was converted to paroxetine hydrochloride in 3 steps.



Scheme 2.8 GlaxoSmithKline synthesis



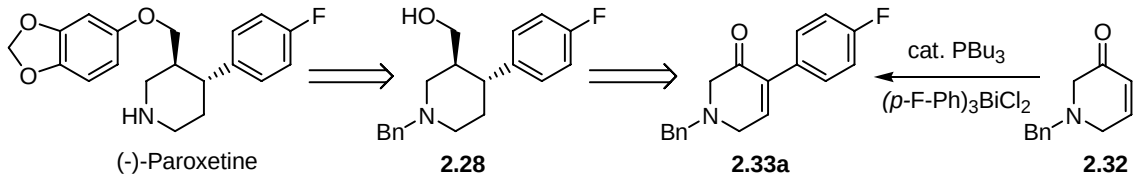
Scheme 2.9 Jacobsen's synthesis

The shortest enantioselective synthesis was reported by Jacobsen and co-workers in 2003.[32] This synthesis employs an enantioselective Michael addition of a nitrile to an aryl substituted α,β-unsaturated imide **2.29** in the presence of the catalyst Salen-Al complex [*S*,*S*]-**A** to provide intermediate **2.30** in excellent yields and excellent enantioselectivity after recrystalization (Scheme 2.9). The intermediate **2.30** was transformed to the amino alcohol **2.31** in 4 steps, and **2.31** was converted to paroxetine hydrochloride in 3 steps. This is an expeditious way for asymmetric synthesis of PAXIL (8 steps), however it involves an epimerization step which makes it less attractive.

Our objective is to show case the synthetic application of our enone arylation methodology. Another goal is to improve on the exist methods for asymmetric synthesis of PAXIL. We hope to cut the number of steps in the GlaxoSmithKline syntheis by half, thus providing the shortest enantioseletive synthesis.

2.4.1 Retrosynthetic Analysis

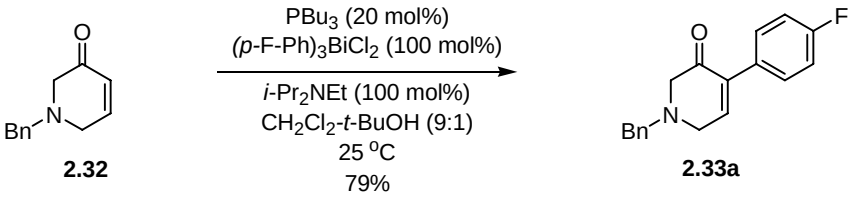
Retrosynthetically, paroxetine is envisioned to derive from *N*-benzylaminoalcohol **2.28**, which could be obtained from α-arylated dihydropyridinone **2.33a** *via* 1,4 reduction followed by Wittig olefination, hydrolysis and carbonyl reduction. The α-arylated dihydropyridinone **2.33a** would arise from dihydropyridinone **2.32** *via* phosphine-catalyzed α-arylation (Scheme 2.10).



Scheme 2.10 Retrosynthetic analysis of (-)-paroxetine

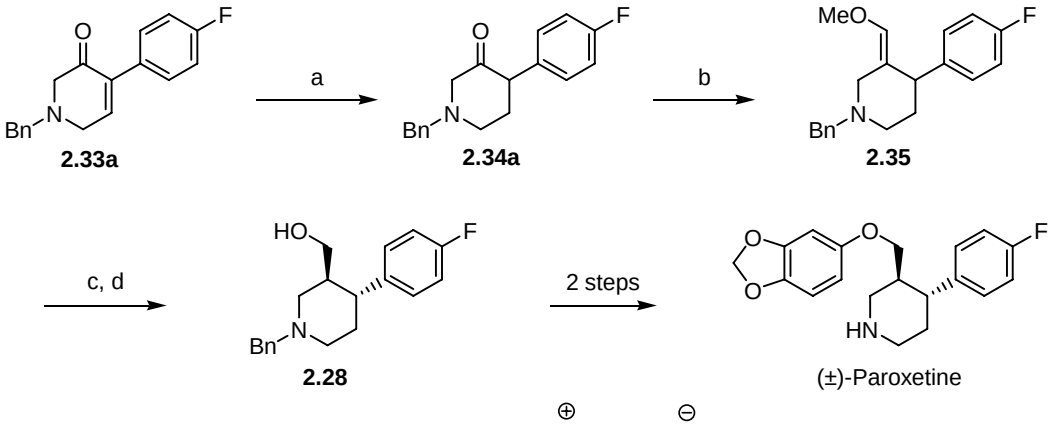
2.4.2 Formal Synthesis of (±)-Paroxetine (PAXIL®)

The forward synthesis begins with dihydropyridinone **2.32** which is prepared from commercially available *N*-benzyl glycine ester in 3 steps.[34] With dihydropyridinone **2.32** in hand, its ability to participate in the phosphine catalyzed α-arylation was examined (Scheme 2.11). Upon exposure to $(p\text{-F-Ph})_3BiCl_2$ (100 mol%), catalytic tributylphosphine (20 mol%), and Hünig's base (100 mol%) at room temperature in CH_2Cl_2–*t*-BuOH (9:1) solvent, aryl transfer proceeds readily to give α-arylated dihydropyridinone **2.33a** in 79% isolated yield as a single regioisomer, based on ^1H NMR analysis.



Scheme 2.11 Catalytic α-arylation of dihydropyridinone **2.32**

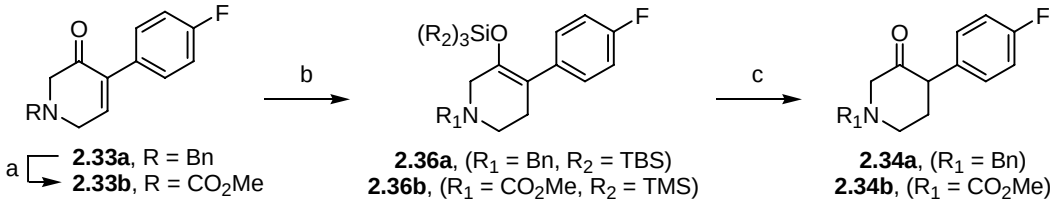
Elaboration of α-aryldihydropyridinone **2.33a** to *N*-benzylamino alcohol **2.28**, a common intermediate in synthesis of paroxetine, is achieved in 4 manipulations. L-Selectride reduction[35] of **2.33a** occurs in 87% yield to provide the *N*-benzylamino ketone **2.34a**. Wittig olefination of *N*-benzylamino ketone **2.34a** affords enol ether **2.35** in 65% yield with single olefin geometry as determined by ^{1}H NMR. Acid hydrolysis of **2.35** followed by $NaBH_4$ reduction of the resulting aldehyde provides the *N*-benzylamino alcohol **2.28** in 63% yield as a single stereoisomer. *N*-benzylamino alcohol **2.28** exhibits spectral properties identical in all aspects as previously reported material, which has been converted to paroxetine in 2 steps.[28i,29e,31b,c,33] Thus, the synthesis of **2.28** represents a formal synthesis of (±)-paroxetine (Scheme 2.12).



Scheme 2.12 Conversion of α-aryl dihydropyridinone **2.33a** to (±)-paroxetine

2.4.3 Enantioselective Total Synthesis of (-)-Paroxetine (PAXIL®)

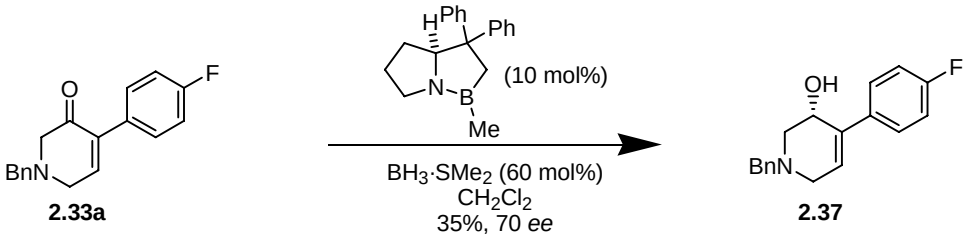
Having completed a formal racemic synthesis of paroxetine, efforts were focused on an enantioselective total synthesis. Here, a potentially effective strategy involves asymmetric protonation[36,37] of enol silanes **2.36a** or **2.36b**, which are derived in a single manipulation from enones **2.33a** and **2.33b** by way of conjugate reduction with trapping of the resulting enolate *in situ* using trimethylsilyl chloride or *tert*-butyldimethylsilyl chloride, respectively.[35] However, enol silane **2.36a** did not react upon exposure to Yamamoto's BINOL-$SnCl_4$ reagent,[36a-c] perhaps due to the presence of the Lewis basic *N*-benzyl amine. Treatment of the carbamoyl-protected enol silane **2.36b** to the BINOL-$SnCl_4$ reagent gave the desired α-arylketone **2.34b** in 80% yield, but with very low levels of optical enrichment (10% ee). Yanagisawa's recently reported silver fluoride catalyzed asymmetric protonation gave a more promising result, providing the α-arylketone **2.34b** in 90% yield and 39% ee (Scheme 13).[36d]



Conditions: (a) MeOCOCl, CH_2Cl_2, 25 °C, 86%. (b) Li(s-Bu)$_3$BH, THF, -78 °C, then R_3SiCl, 74% (TBSCl) and 86% (TMSCl). (c) AgF (cat.), (*R*)-BINAP (cat.), CH_2Cl_2:MeOH (20:1), 90%, 39% ee (refers to the conversion of **2.36b** to **2.34b**).

Scheme 2.13 Attempted asymmetric protonation of enol silanes **2.36a** and **2.36b**

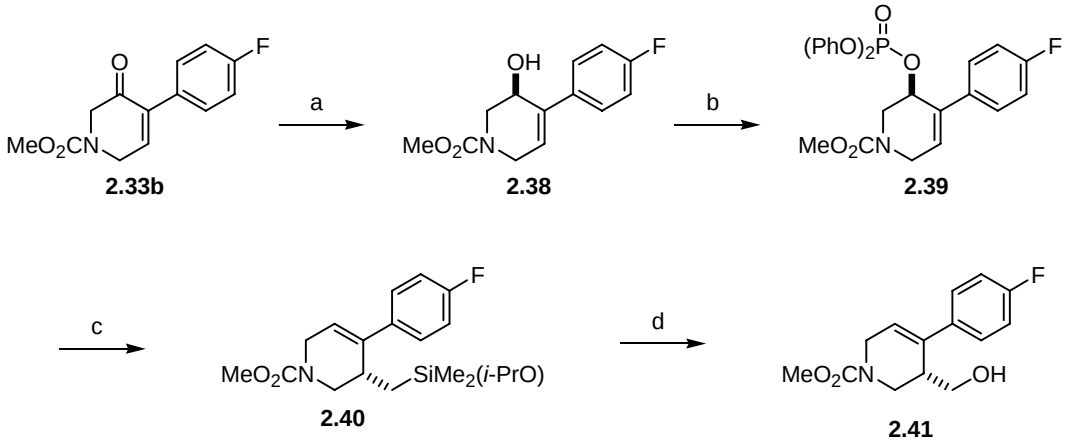
The difficulties encountered in preparing optically enriched aminoketones **2.34a** or **2.34b** led us to consider alternative synthetic routes. Accordingly, oxazaborolidine-catalyzed asymmetric 1,2-reduction of enones **2.33a** and **2.33b** was explored.[38] The *N*-benzyl protected enone **2.33a** gave the corresponding allylic alcohol **2.37** in 35% yield and 70% ee (Scheme 2.14). It was speculated that the presence of the Lewis basic *N*-benzyl amine of **2.33a** was incompatible with the Lewis acidic oxazaborolidine catalyst, resulting in diminished yields and selectivities.



Scheme 2.14 Oxazaborolidine reduction of **2.33a**

Gratifyingly, oxazaborolidine-catalyzed asymmetric 1,2-reduction of the corresponding *N*-carbamoyl protected enone **2.33b** provides allylic alcohol **2.38** in 95% yield and 96% enantiomeric excess (Scheme 2.15). Allylic alcohol **2.38** was converted to the diphenyl phosphate **2.39** and was subjected to conditions for *anti*-selective copper-mediated S_N2' allylic substitution[39] using (*i*-PrO)Me_2SiCH_2MgCl as a hydroxymethyl anion equivalent.[40] The resulting homoallylic silane **2.40** was obtained in 96% yield, and was subjected to Tamao oxidation to provide the homoallylic alcohol **2.41** in 70% yield. As revealed by chiral stationary phase HPLC analysis, compound **2.41** is obtained in 92% enantiomeric excess. The high fidelity of chirality transfer supports the *anti*-S_N2'

mechanism for allylic substitution and the slight decrease in enantiomeric excess is attributed to competitive S_N2 substitution.

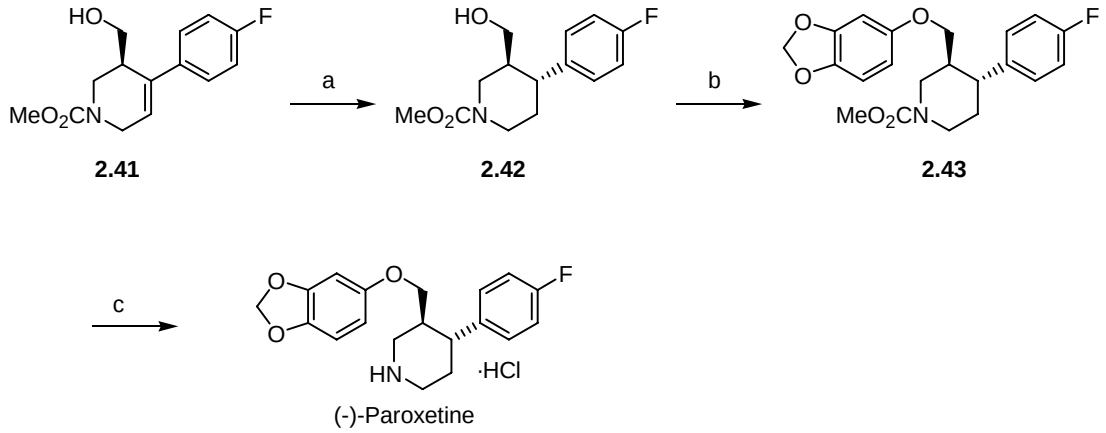


2.33b **2.38** **2.39** **2.40** **2.41**

Conditions: (a) (S)-Me-CBS (cat), $BH_3{\cdot}SMe_2$, CH_2Cl_2, -20 °C, 95%, 96% ee. (b) $(PhO)_2P(O)Cl$, DMAP (cat.), Pyr, CH_2Cl_2, 25 °C, 89%. (c) (*i*-PrO)Me_2SiCH_2Cl, Mg, 25 °C, then CuCN, THF, -30 to 0 °C, 96%. (d) KF, H_2O_2, DMF, 25 °C, 70%, 92% ee.

Scheme 2.15 Conversion of enone **2.33b** to homoallylic alcohol **2.41**

Stereoselective substrate-directed catalytic homogeneous hydrogenation of the homoallylic alcohol **2.41** was accomplished using Crabtree's conditions[41,42] to provide the corresponding saturated alcohol **2.42** in 69% yield as a single diastereomer as determined by ^{1}H NMR analysis (Scheme 2.16). The alcohol was converted to the phenolic ether **2.43** in 76% yield through its reaction with sesamol under Mitsunobu conditions.[43] Finally, deprotection of methyl carbamate was achieved under basic conditions,[44] and the amine was isolated as its HCl salt to provide (-)-paroxetine as hydrochloride salt in 92% yield. (-)-Paroxetine hydrochloride obtained in this manner exhibits spectral properties identical in all respects to previously reported material (Scheme 2.16).[28-33]

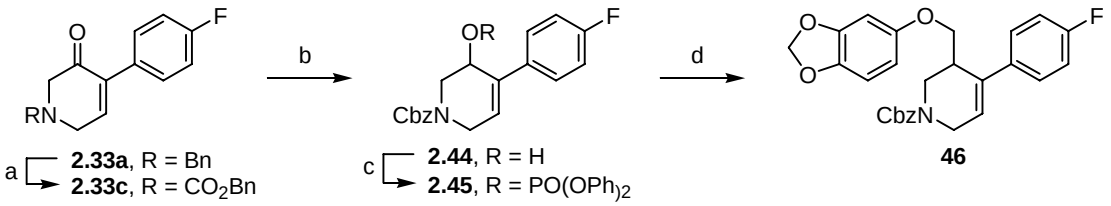


Conditions: (a) $[Ir(COD)(PCy_3)Pyr]PF_6$, CH_2Cl_2, 25 °C, 69%. (b) DIAD, PPh_3, sesamol, THF, 0 to 50 °C, 76%. (c) KOH, $(HOCH_2)_2$, 100 °C, then HCl, 92%.

Scheme 2.16 Enantioselective total synthesis of (-)-paroxetine

2.3.5 Attempted Concise Route to (-)-Paroxetine

A more concise approach to (-)-paroxetine is potentially achieved *via* direct *anti*-selective copper-mediated S_N2' allylic substitution using a sesamol-based phenoxymethyl anion. Stimulated by this prospect, the tributylstannylmethyl ether was prepared from sesamol and tributyl(iodomethyl)stannane. [45] Allylic substitution using the phenoxymethyl anion derived cuprate with allylic phosphate **2.33c** gave the desired phenolic ether in 27% yield. This low yield is attributed to the instability of the intermediate α-alkoxy organolithium reagent and the resulting organocuprate with respect to α-elimination, as evident by the recovery of sesamol. Hence, this strategy was not implemented in the synthesis of (-)-paroxetine (Scheme 2.17).



Conditions: (a) BnOCOCl, CH_2Cl_2, 25 °C, 89%. (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, CH_3OH, 25 °C, 76%. c) $(PhO)_2P(O)Cl$, DMAP (cat.), Pyr, CH_2Cl_2, 25 °C, 86%. (d) Ar-OCH_2SnBu_3, BuLi, THF, -78 °C, then $CuBr \cdot SMe_2$, THF, -78 to -10 °C, 27%.

Scheme 2.17 Attempted concise approach to (-)-paroxetine

2.5 Summary and Concluding Remarks

Cylic enones, β–substituted enals, and aromatic nitroalkenes undergo regiospecific α-arylation under the conditions of nucleophilic catalysis using triarylbismuth(V) dichlorides. This transformation is a regiochemical complement to Heck arylation. The preservation of the alkene moiety in the product facilitates further functionalization of the arylated products. The drawbacks to this method include the transfer of only one aryl group from the triarylbismuth(V) reagent, inability to transfer ortho-substituted arenes, and diminished yields on transferring electron rich aryl groups. This method has been strategically applied in a concise formal and enantioselective total synthesis of the antidepressant (-)-paroxetine (PAXIL). Future studies will focus on the invention of related reagents for efficient aryl, heroaryl, and alkyl transfer under the conditions of nucleophilic catalysis.

2.6 Experimental Section

General

All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe. Flasks were oven-dried and cooled under a stream of argon. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium turnings and iodine. Ethyl acetate was distilled from magnesium sulfate. Tributylphosphine was distilled at reduced pressure and stored under inert atmosphere. Other solvents and chemical reagents obtained from commercial sources were used without further purification, unless otherwise noted. Triarylbismuth dichloride reagents were prepared according to literature procedure.[18] All known products exhibited spectral properties consistent with literature reports **2.17a**,[46] **2.17b**,[47] **2.17h**,[48] **2.18a**,[49] **2.18b**,[50] **2.18c**,[51] **2.18d**,[52] **2.19a**,[53] **2.19b**,[54] and nitroalkenes **2.21a-2.25a** were prepared according to reported literature procedures **2.21a-2.22a**,[55] **2.23a**,[56] **2.24a**,[57] and **2.25a**.[58]The arylation product **2.20b** exhibited spectral properties consistent with previously reported data.[59] Dihydropyridinone **2.32** was prepared from *N*-benzyl glycine ethyl ester according to literature procedures.[34] The *E*/*Z* product ratios were determined by proton nuclear magnetic resonance (^{1}H NMR). Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Krieselgel 60 F_{254}). Preparative column chromatography employing silica gel was performed according to the method of Still.[60] Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer 1420 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/e (relative intensity). Accurate masses are reported for the molecular ion (M+1) or a suitable fragment ion.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (300 MHz) spectrometer and a Mercury (400 MHz) spectrometer. Chemical Shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini 300 (75.5 MHz) spectrometer and a Mercury 400 (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the center of the triplet at 77.00 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadbrand decoupling.

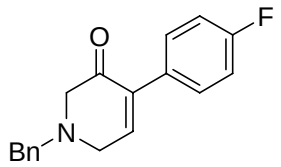
Representative Procedure for α-Arylation of Enones 2.17-2.18 and Enal 2.19

To a reaction vessel charged with triphenylbismuth dichloride (261 mg, 0.52 mmol, 100 mol%) and 2-cyclohexen-1-one **2.17** (50μL, 0.52 mmol, 100 mol%) was added CH_2Cl_2-*t*-BuOH (9:1 ratio, 0.52 mL, 1M), followed by diisopropylethylamine (90μL, 0.52 mmol, 100 mol%) and tributylphosphine (25μL, 0.10 mmol, 20 mol%). The reaction mixture was allowed to stir at room temperature until complete consumption of triphenylbismuth dichloride was observed by TLC (2-12 hours), at which point the reaction mixture was evaporated onto SiO_2. Purification by silica gel chromatography hexane/ethyl acetate 9:1 gave **2.17a** (0.083g, 93%) as a white solid.

Representative Procedure for α-Arylation of Nitroalkenes 2.20a-2.25a

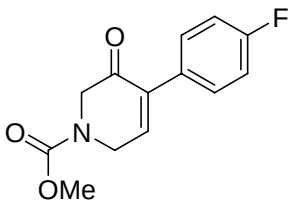
To a clean dry 13 X 100 test tube charged with β-nitrostyrene **2.20a** (50mg, 0.33 mmol, 100 mol%) and Ar_3BiCl_2 (0.35g, 0.67 mmol, 200 mol%) was added EtOAc (0.7 mL, 0.5M), followed by tributylphosphine (17μL, 0.067 mmol, 20 mol%) and diisopropylethylamine (60 μL, 0.33 mmol, 100 mol%). The reaction vessel was place into a preheated oil bath (50 °C) and the reaction was allowed to stir at this temperature until complete consumption of the starting material was observed by TLC analysis (3h). The reaction vessel was removed from the heating oil bath and allowed to cool to room temperature, at which point a solution of 50% aqueous Na_2CO_3 (2 mL) was added and allowed to stir for 10 min, this step enables conversion of excess Ph_3BiCl_2 to the more polar and insoluble Ph_3BiCO_3 which can easily isolated. The resulting mixture was filtered through celite, washed three times with Et_2O (5 mL), the filtrate was extracted with Et_2O (3 X 5 mL), the organic extracts were combined, dried over $MgSO_4$, filtered and evaporated onto silica gel. Purification *via* column chromatography (SiO_2, 19:1 to 3:2 hexane/ethyl acetate) gives the α-arylation product **2.20b** (51 mg, 0.22 mmol) in 67% yield as an off white solid.

Preparation of Compounds 2.33a- 2.46



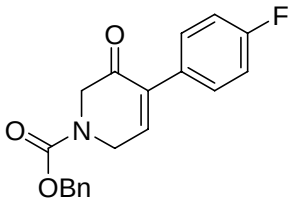
1-Benzyl-4-(4-fluorophenyl)-1,6-dihydro-*2H*-pyridin-3-one 2.33a

To 100 mL flask charged with tris-(4-fluorophenyl)bismuth dichloride (12.3 g, 21.75 mmol, 110 mol%) and **2.32** (3.7 g, 19.77 mmol, 100 mol%) was added CH_2Cl_2-*t*-BuOH (9:1), (36 mL, 0.5M), followed by tributylphosphine (0.5 mL, 1.99 mmol, 10 mol%) and diisopropylethylamine (3.4 mL, 19.78 mmol, 100 mol%). The reaction mixture was allowed to stir at room temperature until complete consumption of starting material was observed by TLC (3 h), at which point the reaction mixture was evaporated onto silica gel. Purification by column chromatography (SiO_2, 9:1 to 3:2 hexane/ethyl acetate) gives the title compound **2.33a** (4.39 g, 15.60 mmol) in 79% yield as an off white solid. Mp 66.5-68.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (m, 6H), 7.03 (m, 4H), 3.70 (s, 2H), 3.43 (d, J = 3.42 Hz, 2H), 3.33 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 162.5 (d, J = 247.5 Hz), 145.2, 137.4, 136.3, 130.8, 130.2 (d, J = 8.5 Hz), 129.1, 128.5, 127.6, 114.9 (d, J = 21.5 Hz), 61.8, 61.7, 52.6. IR (film): 3063, 3029, 2918, 2803, 2750, 1683, 1601, 1509, 1349, 1223, 1160, 823, 699 cm^{-1}. HRMS: Calcd for $C_{18}H_{17}NOF$ [M+1] 282.1294, found 282.1289.



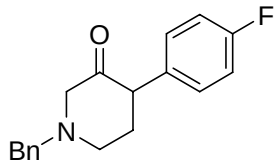
4-(4-Fluorophenyl)-3-oxo-3,6-dihydro-*2H*-pyridine-1-carboxylic acid methyl ester enone 2.33b

Methylchloroformate (2 mL, 24.91 mmol, 200 mol%), was added dropwise to a solution containing **2.33a** (3.5 g, 12.45 mmol, 100 mol%) in CH_2Cl_2 (20 mL) at room temperature. The reaction mixture was stirred at this temperature for 18h, at which point the reaction mixture was evaporated onto silica gel and purified *via* column chromatography (SiO_2, 4:1 to 1:1 hexane/ethyl acetate) to give the title compound **2.33b** (2.64 g, 10.55 mmol) in 86% yield as a white solid. Mp 110-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.05 (t, *J* = 8.6 Hz, 3H), 4.45 (d, *J* = 2.1 Hz, 2H), 4.29 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 162.1 (d, *J* = 247.5 Hz), 155.3, 143.4, 137.2, 130.1 (d, *J* = 3.1 Hz), 130.2 (d, *J* = 7.7 Hz), 115.1 (d, *J* = 21.5 Hz), 53.0, 51.9, 43.6. IR (film): 3053, 2981, 2863, 1723, 1673, 1606, 1463, 1403, 1351, 1236, 1103, 953, 842, 809 cm^{-1}. HRMS: Calcd for $C_{13}H_{13}NO_3F$ [M+1] 250.0879, found 250.0882.



4-(4-Fluorophenyl)-3-oxo-3,6-dihydro-*2H*-pyridine-1-carboxylic acid benzyl ester 2.33c

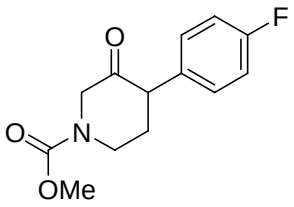
Benzylchloroformate (1.21 g, 7.12 mmol, 200 mol%) and **2.33a** (1 g, 3.56 mmol, 100 mol%) were reacted according to the procedure described for **2.33b**. The crude product was purified *via* column chromatography (SiO_2, 4:1 to 1:1 hexane/ethyl acetate) to give compound **2.33c** (1.03 g, 3.16 mmol) in 89% yield as a white solid. Mp 80-81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (m, 5H), 7.31 (dd, *J* = 8.9, 5.5 Hz, 2H), 7.04 (t, *J* = 8.9 Hz, 2H), 5.19 (s, 2H), 4.47 (d, *J* = 3.8 Hz, 2H), 4.32 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 162.7 (d, *J* = 247.5 Hz), 154.7, 143.3, 137.2, 135.8, 130.3 (d, *J* = 7.7 Hz), 128.5, 128.2 (d, *J* = 6.9 Hz), 115.1 (d, *J* = 21.5 Hz), 67.8, 51.9, 43.6. IR (film): 3033, 2956, 2829, 1688, 1601, 1509, 1430, 1350, 1231, 1160, 1100, 814 cm^{-1}. HRMS: Calcd for $C_{19}H_{17}NO_3F$ [M+1] 326.1192, found 326.1195.



1-Benzyl-4-(4-fluorophenyl)piperidin-3-one 2.34a

To a solution containing **2.33a** (0.71 g, 2.53 mmol, 100 mol%) in dry THF (15 mL) at -78 °C was added L.Selectride (1M in THF 2.6 mL, 2.53 mmol, 100 mol%) dropwise. The mixture was stirred at -78 °C for 1h, at which point aqueous NH_4Cl (10%

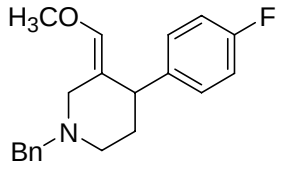
solution, 20 mL) was added. The reaction mixture was transferred to a separatory funnel and was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated in *vacuo* to afford an oily residue. Purification by column chromatography (SiO_2, 9:1 to 3:2 hexane/ethyl acetate) gives compound **2.34a (**0.609 g, 2.15 mmol) in 87% yield as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 5H), 7.11 (m, 2H), 7.03 (m, 2H), 3.64 (s, 2H), 3.53 (t, *J* = 10.0 Hz, 1H), 3.36 (dd, *J* = 14.1, 1.8 Hz, 1H), 3.06 (dm, *J* = 9.2 Hz, 1H), 2.93 (d, *J* = 13.8 Hz, 1H), 2.58 (m, 1H), 2.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.2, 162.2 (d, *J* = 246.2 Hz), 136.9, 133.65, 130.2 (d, *J* = 8.4 Hz), 129.0, 128.4, 127.4, 115.3 (d, *J* = 11.5 Hz), 64.4, 62.5, 54.3, 51.9, 32.7. IR (film): 3062, 3029, 2949, 2801, 1722, 1604, 1511, 1454, 1224, 1098, 833, 740, 700 cm^{-1}. HRMS: Calcd for $C_{18}H_{19}NOF$ [M+1] 284.1450, found 284.1454.



4-(4-Fluorophenyl)-3-oxo-piperidine-1-carboxylic acid methyl ester 2.34b

A mixture of silver fluoride (2 mg, 16 μmol, 10 mol%) and (*R*)-BINAP (5.8 mg, 9 μmol, 6 mol%) was dissolved in methanol (0.2 mL) and stirred at room temperature for 10 min in the dark. At which point CH_2Cl_2 (2 mL) was added and the solution was stirred for another 10 min. The solution was cooled to -78 °C and **2.36b** (50 mg, 0.15 mmol, 100 mol%) in dichloromethane (2 mL) was added dropwise. The mixture was warmed to -30

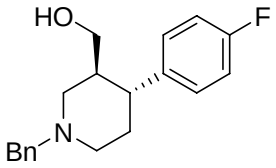
°C and stirred at this temperature for 72h, at which point the mixture was evaporated to dryness. Purification *via* column chromatography (SiO_2, 4:1 to 1:1 hexane/ethyl acetate) gives the title compound **2.34b** (35 mg, 0.014 mmol) in 90% yield as colorless oil. Chiral HPLC (Daicel Chiralpak OJ-H column, 85:15 hexanes:*i*-PrOH, λ = 254 nm, 0.5 mL/min, t_{major} = 67.0 min, t_{minor} = 97.7 min *ee* = 39%). ^{1}H NMR (500 MHz, DMSO-d_6 @ 100 °C): δ 7.19 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.10 (t, *J* = 11.1 Hz, 2H), 4.14 (A part of AB pattern, d, *J* = 17.4 Hz, 1H), 4.05 (B part of AB pattern, d, *J* = 17.4 Hz, 1H), 3.85 (m, 2H), 3.63 (s, 3H), 3.56 (m, 2H), 2.21 (m, 2H). ^{13}C NMR (125 MHz DMSO-d_6 @ 100 °C): δ 203.9, 160.7 (d, *J* = 243.1 Hz), 154.7, 133.3 (d, *J* = 3.5 Hz), 129.2 (d, *J* = 8.1 Hz), 114.2 (d, *J* = 1.3 Hz), 53.2, 51.9, 41.7, 29.1. IR (film): 2956, 1700, 1602, 1511, 1449, 14404, 1223, 835 770 cm^{-1}. HRMS: calcd for $C_{13}H_{15}NO_3F$ [M+1] 252.1036, found 252.1038.



1-Benzyl-4-(4-fluorophenyl)-3-methoxymethylene piperidine 2.35

To a vigorously stirred suspension of methoxymethyltriphenylphosphonium chloride[61] (0.5 g, 1.76 mmol, 100 mol%) in dry THF (18 mL) was added a solution of NaHMDS (2M in THF 3.5 mL, 7.06 mmol, 400 mol%) dropwise. The resulting red solution was stirred at this temperature for 2h, at which point **2.34a** (0.5g, 1.76 mmol, 100 mol%) in THF (3 mL) was added dropwise over 10 min. The reaction mixture was stirred at room temperature for 20h, at which point aqueous NH_4Cl (1M, 30 mL) was

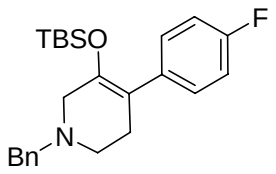
added. The resulting mixture was extracted with diethyl ether (3 x 15 mL) and the combined organics were combined, dried ($MgSO_4$), filtered and evaporated in *vacuo* to give a yellow oil. Purification of the residue *via* column chromatography (SiO_2, 9:1 to 4:1 hexane/ethyl acetate) gives the title compound **2.35** (0.35g, 11.29 mmol) in 65% yield as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 5H), 7.19 (m, 2H), 6.99 (t, *J* = 8.9 Hz, 2H), 5.14 (s, 1H), 3.83 (d, *J* = 12.3 Hz, 1H), 3.70 (A part of AB pattern, *J* = 13.0 Hz, 1H), 3.50 (B part of AB pattern, *J* = 13.0 Hz, 1H), 3.42 (s, 3H), 3.16 (d, *J* = 10.3 Hz, 1H), 2.90 (d, *J* = 11.6 Hz, 1H), 2.60 (d, *J* = 12.3 Hz, 1H), 2.21 (td, *J* = 11.3, 2.7, 1H), 1.98 (m, 1H), 1.78 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4 (d, *J* = 244.4 Hz), 143.2, 137.9, 137.7, 129.8 (d, *J* = 7.6 Hz), 129.4, 128.1, 126.9, 117.5, 114.9 (d, *J* = 21.1 Hz), 63.0, 59.4, 52.8, 51.6, 43.9, 32.7. IR (film): 3029, 2933, 2846, 2798, 1677, 1603, 1509, 1222, 1129, 835, 699 cm^{-1}. HRMS: Calcd for $C_{20}H_{22}NOF$ [M +1] 311.1685, found 311.1675.



[1-Benzyl-4-(4-fluorophenyl)piperidin-3-yl]methanol 2.28

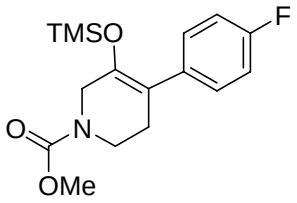
A solution of the enol ether **2.35** (50 mg, 0.16 mmol, 100 mol%) in THF (3 mL), was treated with 0.1M aqueous H_2SO_4 (2.4 mL, 0.24 mmol, 150 mol%). The solution was allowed to reflux for a 12h period, at which point the heating bath was removed and the reaction was allowed to reach room temperature. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the resulting mixture was extracted with diethyl ether (3 x 5 mL). The

combined organics extracts were dried ($MgSO_4$), filtered and evaporated in *vacuo* to provide the crude aldehyde (34 mg, 0.11 mmol) in 72 % yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.45 (d, *J* = 1.8 Hz, 1H), 7.34 (m, 5H), 7.28 (m, 2H), 7.02 (t, *J* = 8.5 Hz, 2H), 3.62 (s, 2H), 3.18 (dm, *J* = 11.4 Hz, 1H), 2.99 (dm, *J* = 11.4 Hz, 1H), 2.90 (dm, *J* = 18.4 Hz, 1H), 2.77 (dd, *J* = 9.0, 7.0 Hz, 1H), 2.12 (t, *J* = 11.1 Hz, 2H), 1.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.0, 161.6 (d, *J* = 244.7 Hz), 138.6, 137.8, 129.1, 128.8 (d, *J* = 7.9 Hz), 128.3, 127.2, 115.5 (d, *J* = 21.4 Hz), 63.1, 54.4, 53.5, 53.0, 43.1, 34.1. IR (film): 2938, 2806, 1721, 1603, 1510, 1465, 1224, 1160, 833, 699 cm^{-1}. HRMS: Calcd for $C_{19}H_{21}NOF$ [M+1] 298.1607, found 298.1601. The crude aldehyde was dissolved in ethanol (2 mL) and treated with $NaBH_4$ (6 mg, 0.16 mmol, 100 mol%): The reaction mixture was stirred at room temperature for 1h. The reaction mixture was treated with 2N aqueous sodium hydroxide (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL), and combined organic extracts were dried ($MgSO_4$), filtered and evaporated in *vacuo* to give an oily residue. Purification of the residue *via* column chromatography (SiO_2, 9:1 to 3:2 hexane/ethyl acetate) gives the title compound **2.28** (30 mg, 0.10 mmol) in 63% yield over two steps as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 5H), 7.17 (m, 2H), 6.98 (t, *J* = 8.6 Hz, 2H), 3.60 (A part of AB pattern, *J* = 13.2 Hz, 1H), 3.56 (B part of AB pattern, *J* = 13.2 Hz, 1H), 3.37 (dd, *J* = 11.3, 3.0 Hz, 1H), 3.21 (m, 2H), 2.98 (d, *J* = 11.0 Hz, 1H), 2.33 (m, 1H), 1.98 (m, 3H), 1.79 (m, 3H). IR (film): 3427, 2934, 2848, 2799, 1604, 1510, 1222, 1130, 836, 739, 700cm^{-1}. HRMS: Calcd for $C_{19}H_{23}NOF$ [M+1] 300.1763, found 300.1748.



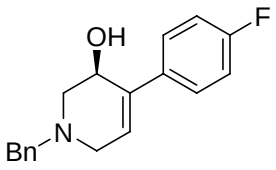
1-Benzyl-5-(*tert*-butyldimethylsilanyloxy)-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine 2.36a

To a solution containing **2.33a** (0.1 g, 0.35 mmol, 100 mol%) in dry THF (2 mL) at -78 °C was added L-Selectride (1M in THF 0.36 mL, 0.35 mmol, 100 mol%) dropwise. The mixture was stirred at this temperature for 1h, upon which TBSCl (59 mg, 0.39 mmol, 110 mol%) in THF (1 mL) was added dropwise. The reaction mixture was allowed to stir at this temperature for an additional 1h and then left to warm to room temperature. Evaporation of the reaction mixture in *vacuo* affords an oily residue that was purified by column chromatography (SiO_2, 9:1 hexane/ethyl acetate) to give **2.36a** (0.104 g, 2.62 mmol) in 74% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 7H), 6.95 (t, *J* = 8.7 Hz, 2H), 3.63 (s, 2H), 2.99 (s, 2H), 2.63 (t, *J* = 5.6 Hz, 2H), 2.43 (m, 2H), 0.74 (s, 9H), -0.19 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1 (d, *J* = 243.5 Hz), 140.8, 130.1 (d, *J* = 7.6 Hz), 129.3, 128.3, 114.6 (d, *J* = 21.1 Hz), 62.2, 56.3, 50.1, 29.2, 25.5, 17.9, -4.2. IR (film): 2928, 2856, 1669, 1601, 1509, 1471, 1222, 837, 780 cm^{-1}. HRMS: calcd for $C_{24}H_{33}NOFSi$ [M+1] 398.2315, found 398.2313.



4-(4-Fluorophenyl)-5-trimethylsilanyloxy-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester 2.36b

Aryl enone **2.33b** (0.2 g, 0.80 mmol, 100 mol%), L-selectride (1M in THF 0.8 mL, 0.80 mmol, 100 mol%) and chlorotrimethylsilane (0.12 mL, 0.88 mmol, 110 mol%) were reacted according to the procedure described for **2.36a**. The crude product was purified *via* Kugelrohr distillation to give **2.36b** (0.23 g, 0.71 mmol) in 86% yield as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (dd, *J* = 8.2 Hz, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 3.91 (s, 2H), 3.73 (s, 3H), 3.60 (s, 2H), 2.43 (s, 2H), -0.04 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.0, 161.2 (d, *J* = 245.0 Hz), 155.8, 140.8, 135.2, 129.8 (d, *J* = 7.6 Hz), 114.5 (d, *J* = 21.4 Hz), 52.6, 46.8, 41.0, 28.5, 0.3. IR (film): 2957, 1707, 1601, 1510, 1448, 1410, 1253, 1226, 1106, 844, 767 cm^{-1}. HRMS: Calcd for $C_{16}H_{23}NO_3FSi$ [M+1] 324.1431, found 324.1437.

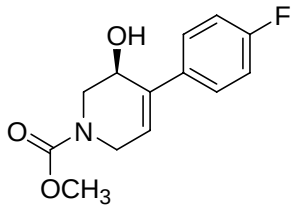


1-Benzyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridin-3-ol 2.37

To a solution of **2.33a** (0.1 g, 0.35 mmol, 100 mol%) in CH_2Cl_2 (3.5 mL) and isopropyl alcohol (30 μL, 0.35 mmol, 100 mol%) at -20 °C was added dropwise a solution of

$BH_3 \bullet SMe_2$ (2M in THF 0.45 mL, 0.89 mmol, 250 mol%). The mixture was stirred at -20 °C for 1h, at which point a solution containing both (*S*)-2-Methyl-CBS-oxazaborolidine (2M in toluene 36 μL, 35 μmol, 10 mol %) and a solution of $BH_3 \bullet SMe_2$ (2M in THF, 30 μL) was added in one portion. The reaction mixture was allowed to stir at -20 °C for 30 min. The temperature was increased to -15 °C over 45 min, at which point MeOH (10 mL) was added carefully, and the reaction mixture was allowed to stir for an additional 15 min. The reaction mixture was placed in a heating bath at 50 °C and CH_2Cl_2 and $BH_3 \bullet SMe_2$ were removed *via* distillation. To the remaining solution was added MeOH (5 mL) and the resulting mixture was allowed to stir 65 °C for 1h (to break the N-B complex). The heating bath was removed and the reaction mixture was allowed to reach ambient temperature. The solvent was removed in *vacuo* and the resulting residue was purified *via* column chromatography (SiO_2, 3:2 to 1:1 hexane/ethyl acetate) to provide the allylic alcohol **2.37** (36 mg, 0.13 mmol) in 35% yield as a white solid. Mp 76-77 °C. Chiral HPLC (Daicel Chiralpak OJ-H column, 98:2 hexanes:*i*-PrOH, λ = 254 nm, 1 mL/min, t_{major} = 43.9 min, t_{minor} = 31.7 min *ee* = 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.33 (m, 5H), 6.99 (t, *J* = 8.9 Hz, 2H), 6.09 (t, *J* = 3.5 Hz, 1H), 6.02 (dd, *J* = 4.8, 3.4Hz, 1H), 4.37 (s, 1H), 3.65 (s, 2H), 3.35 (dd, *J* = 17.4, 4.4 Hz, 1H), 3.04 (dd, *J* = 10.6, 2.0 Hz, 1H), 2.84 (d, *J* = 17.4, 1H), 2.75 (br s, 1H), 2.49 (dd, *J* = 11.6, 2.0 Hz, 1H). ^{13}C NMR (100 MHz $CDCl_3$): δ 162.1 (d, *J* = 246.0 Hz), 137.6, 137.0, 135.2 (d, *J* = 3.1 Hz), 129.0, 128.3, 127.3, 127.1 (d, *J* = 7.7 Hz), 124.5, 115.2 (d, *J* = 21.5 Hz), 66.1, 62.2, 57.7, 53.0. IR (film): 3408, 3061, 3029, 2917, 2804, 1602, 1509,

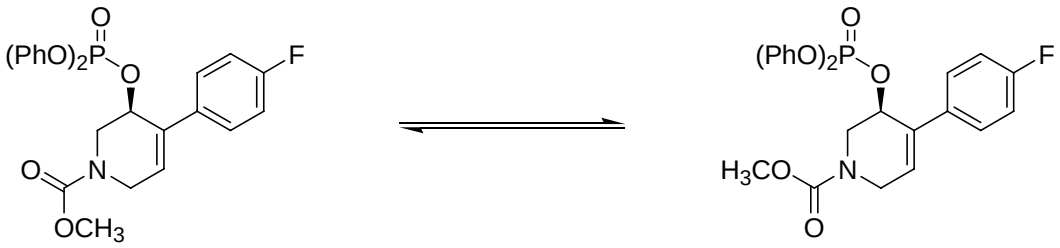
1454, 1230, 1162, 1054, 822, 699. HRMS: Calcd for $C_{18}H_{19}NOF$ [M+1] 284.1450, found 284.1432.



4-(4-Fluorophenyl)-3-hydroxy-3,6-dihydro-*2H*-pyridine-1-carboxylic acid methyl ester 2.38

To a dry 50 mL flask, a solution of (*S*)-2-Methyl-CBS-oxazaborolidine catalyst (1M in toluene 0.4 mL, 0.04 mmol, 10 mol %) and a solution of borane dimethyl sulfide-complex (2M in THF 2 mL, 4.00 mmol, 100 mol%) were added successively at room temperature. The resulting solution was cooled to -20 °C and **2.33b** (1 g, 4.00 mmol, 100 mol%) in CH_2Cl_2 (18 mL) was added dropwise over 1h, the reaction mixture was maintained at this temperature for 1h. Methanol (15 mL) was added dropwise to the reaction mixture and allowed to warm to room temperature. The solution was evaporated to dryness and purification *via* column chromatography (SiO_2, 9:1 to 1:1 hexane/ethyl acetate) gives **2.38** (0.96 g, 3.85 mmol) in 95% yield as a white solid. Mp 104-105 °C; $[\alpha]_D^{25}$ +70° (c =1.6 CH_2Cl_2), chiral HPLC (Daicel Chiralpak OJ-H column, 70:30 hexanes:*i*-PrOH, λ = 254 nm, 0.5 mL/min t_{major} = 35.2 min, t_{minor} = 39.2 min *ee* = 96%) ^{1}H NMR (500 MHz, DMSO-d_6 @ 100 °C): δ 7.52 (dd, *J* = 8.9, 5.5 Hz, 2H), 7.10 (t, *J* = 12.0 Hz, 2H), 6.08 (t, *J* = 3.5 Hz, 1H), 4.79 (d, *J* = 6.6 Hz , 1H), 4.46 (m, 1H), 4.23 (dd, *J* = 19.0, 2.7 Hz, 1H), 3.86 (dd, *J* = 13.3, 3.8 Hz, 1H), 3.84 (dt, *J* = 17.2, 2.0 Hz, 1H),

3.65 (s, 3H), 3.34 (dd, *J* = 13.3, 3.3 Hz, 1H). ^{13}C NMR (125 MHz DMSO-d_6 @ 100 °C): δ 161.0 (d, *J* = 244.1 Hz), 155.1, 136.4, 135.2 (d, *J* = 3.05 Hz), 127.2 (d, *J* = 8.1 Hz), 122.6, 114.2 (d, *J* = 20.8 Hz), 63.0, 51.5, 47.9, 42.9. IR (film): 3412, 2957, 2921, 2851, 1693, 1601, 1511, 1470, 1448, 1411, 1231, 1130, 1062, 818, 767 cm^{-1}. HRMS: calcd for $C_{18}H_{17}NOF$ [M+1] 250.0879, found 250.0880.

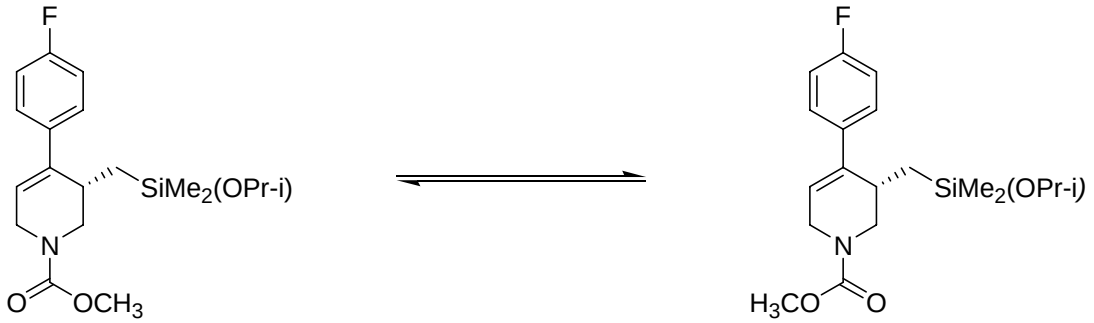


3-(Diphenoxyphosphoryloxy)-4-(4-fluorophenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester 2.39

(Mixture of rotomers)

Chlorodiphenylphosphate (0.9 ml, 4.22 mmol, 150 mol%) was added dropwise to a solution containing **2.38** (0.71 g, 2.81 mmol, 100 mol%), pyridine (0.45 mL, 5.62 mmol, 200 mol%) and DMAP (0.51 g, 4.22 mmol, 150 mol%) at room temperature. After stirring the reaction mixture for 2h at this temperature, it was poured into a separatory funnel, washed with 2M aqueous $CuSO_4$ solution (3 x 20 mL), dried over $MgSO_4$, filtered and evaporated to afford an oily residue. Purification *via* column chromatography (SiO_2, 9:1 to 4:1 dichloromethane/ethyl acetate) gives **2.39** (1.21 g, 2.42 mmol) in 89% yield as a white solid. Mp 99-100 °C. $[\alpha]_D^{23}$ +36° (c = 3.33, CH_2Cl_2), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 4H), 7.18 (m, 6H), 6.94 (t, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 7.94 Hz, 2H),

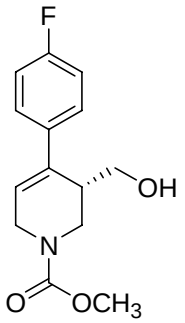
6.22 (s, 1H), 5.62 (s, 1H), 4.55 (dd, *J* = 14.6, 2.8 Hz, 2H), 3.91 (d, *J* = 18.2 Hz, 1H), 3.76 (s, 1H), 3.61 (s, 2H), 3.50 (d, *J* = 14.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5 (d, *J* = 247.3 Hz), 155.9, 150.4, 150.0, 133.4, 129.0 (d, *J* = 16.0 Hz), 127.8, 127.7, 125.2, 125.1, 119.8, 119.7, 115.4 (d, *J* = 21.4 Hz), 71.7, 52.7, 46.4, 43.5. IR (film): 3063, 3033, 2962, 2840, 1706, 1590, 1512, 1488, 1446, 1410, 1283, 1232, 1190, 1130, 1009, 956, 825, 767 cm^{-1}. HRMS: Calcd for $C_{25}H_{24}NO_7FP$ [M+1] 500.1274, found 500.1278.



4-(4-Fluorophenyl)-3-[(isopropoxydimethylsilanyl)methyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester 2.40

To a slurry of CuCN (0.43 g, 4.81 mmol, 200 mol%) in THF (10 mL) was added a solution of (iPrO)Me_2CH_2MgCl (1M in THF 4.80 mL, 4.81 mmol, 200 mol%) at -18 °C (ice/NaCl). After stirring at this temperature for 40 min, the reaction mixture was further cooled to -50 °C and **2.39** (1.20 g, 2.40 mmol, 100 mol%) in THF (10 mL) was added dropwise. The reaction was allowed to warm to 0 °C over 40 min and quenched with 10% aqueous NH_4Cl (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10mL), and the combined organic extracts were dried over $MgSO_4$, filtered and evaporated to afford an oily residue. Purification of the residue *via* column chromatography (SiO_2, 3:2 hexane/ethyl acetate) gives **2.40** (0.84 g, 2.31 mmol) in 96% yield as a colorless oil. $[\alpha]_D$

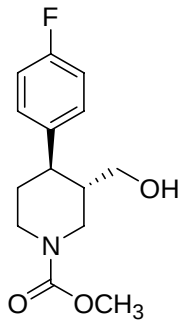
^{23} +72 (*c* = 3.6, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 2H), 6.99 (t, *J* = 8.7 Hz, 2H), 5.76 (s, 1H), 4.28 (m, 1H), 3.95 (m, 2H), 3.87 (d, *J* = 18.8 Hz, 1H), 3.71 (s, 3H), 3.28 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.87 (s, 1H), 1.12 (2d, *J* = 6.2 Hz, 6H), 0.68 (2d, *J* = 10.8 Hz, 1H), 0.55 (2s, 1H), 0.09 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1 (d, *J* = 246.0 Hz), 156.6, 141.6, 135.9, 127.6 (d, *J* = 7.3 Hz), 119.5, 115.1 (d, *J* = 21.1 Hz), 64.9, 52.4, 46.3, 43.8, 32.3, 25.8, 19.5, -0.78. IR (film): 3081, 2956, 2889, 1706, 1601, 1510, 1448, 1412, 1375, 1335, 1250, 1231, 1191, 1118, 1025, 958, 880, 836, 813 cm^{-1}. HRMS: Calcd for $C_{19}H_{27}NO_3FSi$ [M-1] 364.1744, found 364.1745.



4-(4-Fluorophenyl)-3-hydroxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylic acid methyl ester 2.41

To a solution of **2.40** (0.82 g, 2.24 mmol, 100 mol%) in DMF (12 mL) was added potassium fluoride (0.52 g, 8.98 mmol, 400 mol%) and 30% aqueous hydrogen peroxide (3 mL, 26.94 mmol, 1200 mol%) at room. Then after stirring for 18h, it was diluted with water (60 mL). The aqueous layer was extracted with ether (3 x 20 mL) and combined ethereal extracts were washed with saturated aqueous sodium thiosulfate (20 mL), dried over $MgSO_4$ and evaporated to afford colorless oil. Purification *via* column chromatography (SiO_2, 4:1 to 1:1 hexane/ethyl acetate) gives **2.41** (0.41 g, 1.55 mmol) in

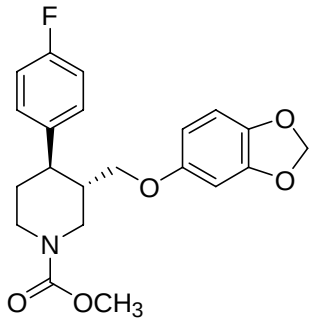
70% yield as a colorless oil. $[\alpha]_D^{23}$ +84° (*c* = 3.06, CH_2Cl_2), chiral HPLC (Daicel Chiralpak OJ-H column, 90:10 hexanes:*i*-PrOH, λ = 254 nm, 0.4 mL/min, t_{major} = 31.0 min, t_{minor} = 45.9 min *ee* = 92%), ^{1}H NMR (500 MHz, DMSO-d_6 @ 100 °C): δ 7.43 (dd, *J* = 8.8, 2.1 Hz, 2H), 7.12 (t, *J* = 8.9 Hz, 2H), 6.00 (t, *J* = 2.4 Hz, 1H), 4.27 (s, 1H), 4.18 (m, 2H), 3.82 (dt, *J* = 19.1, 2.8 Hz, 1H), 3.65 (s, 3H), 3.32 (dt, *J* = 10.6, 3.8, 1H), 3.18 (m, 2H), 2.83 (dd, *J* = 4.2, 2.1 Hz, 1H). ^{13}C NMR (125 MHz DMSO-d_6 @ 100 °C): δ 161.0 (d, *J* = 2.44.1 Hz), 155.3, 135.7 (d, *J* = 3.0 Hz), 135.0, 126.9 (d, *J* = 8.1 Hz), 121.9, 114.4 (d, *J* = 21.4 Hz), 60.3, 51.5, 43.1, 41.5. IR (film): 3426, 3056, 2954, 2876, 1686, 1601, 1510, 1448, 1412, 1375, 1228, 1131, 1091, 1039, 953, 836, 814, 768, 735 cm^{-1}. HRMS: Calcd for $C_{14}H_{17}NO_3F$ [M+1] 266.1192, found 266.1199.



4-(4-Fluorophenyl)-3-hydroxymethylpiperidine-1-carboxylic acid methyl ester 2.42

A solution containing **2.41** (0.3 g, 1.13 mmol, 100 mol%) in CH_2Cl_2 (11 mL) was cooled to -78 °C, evacuated and filled with argon. This process was repeated two more times. The solution was allowed to warm to room temperature and Crabtree's catalyst (45 mg, 0.06 mmol, 5 mol%) was added as a solid in one portion. The mixture was purged with hydrogen for 5 minutes and allowed to stir under hydrogen atmosphere for 20h. The reaction mixture was evaporated onto silica gel and purification *via* column

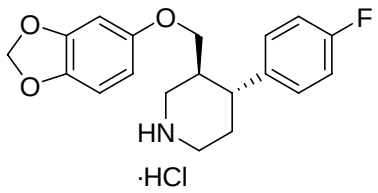
chromatography (SiO_2, 4:1 to 3:2 hexane/ethyl acetate) gives the saturated alcohol **2.42** (0.21 g, 0.79 mmol) in 69% yield. $[\alpha]_D^{23}$ -40° (c = 2.0, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6 @ 100 °C): δ 7.23 (dd, *J* = 7.9, 6.1 Hz, 2H), 7.06 (t, *J* = 8.9 Hz, 2H), 4.30 (dd, *J* = 13.3, 2.5 Hz, 1H), 4.09 (d, *J* = 5.6 Hz, 1H), 4.07 (d, *J* = 15.7 Hz, 1H), 3.64 (s, 3H), 3.18 (m, 1H), 3.02 (m, 1H), 2.83 (t, *J* = 13.0 Hz, 1H), 2.66 (t, *J* = 11.4 Hz, 1H), 2.53 (td, *J* = 11.6, 3.2 Hz, 1H), 1.72 (m, 2H), 1.57 (qd, *J* = 12.6, 4.4 Hz, 1H). ^{13}C NMR (125 MHz DMSO-d_6 @ 100 °C): δ 160.3 (d, *J* = 244.1 Hz), 154.7, 139.8 (d, *J* = 3.0 Hz), 128.5 (d, *J* = 7.6 Hz), 114.3 (d, *J* = 21.4 Hz), 60.8, 51.5, 46.7, 43.6, 43.0, 42.8, 33.2. IR (film): 3435, 3009, 2918, 2853, 1697, 1603, 1510, 1476, 1451, 1413, 1279, 1223, 1159, 1129, 1064, 1014, 832, 767 cm^{-1}. HRMS: Calcd for $C_{14}H_{19}NO_3F$ [M+1] 268.1349, found 268.1350.



3-(Benzo[1,3]dioxol-5-yloxymethyl)-4-(4-fluorophenyl)piperidine-1-carboxylic acid methyl ester 2.43

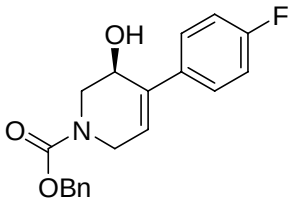
The saturated alcohol **2.42** (0.100 g, 0.37 mmol, 100 mol%) was dissolved in THF (3 mL) and PPh_3 (0.120 g, 0.45 mmol, 120 mol%) was added. This solution was cooled to 0 °C and DIAD (90 μL, 0.45 mmol, 120 mol%) was added dropwise. After stirring this solution at 0 °C for 10 min, sesamol (0.100 g, 0.748 mmol, 200 mol%) in THF (1mL)

was added dropwise, and stirring was continued at 0 °C for another 10 min then warmed to 50 °C for 2h. The reaction mixture was evaporated to dryness, and the resulting residue was dissolved in CH_2Cl_2 (5 mL) and washed with 2M aqueous NaOH (2 x 10mL). The aqueous fractions were combined and back extracted with CH_2Cl_2 (10 mL). The combined organic fractions were evaporated onto silica gel and purification *via* column chromatography (SiO_2, 4:1 hexane/ethyl acetate) gives the phenolic ether **2.43** (0.11 g, 2.84 mmol) in 76% yield as pale yellow oil. $[\alpha]_D^{23}$ -13° (*c* = 1.5, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6 @ 100 °C): δ 7.27 (dd, *J* = 8.6, 5.6 Hz, 2H), 7.06 (t, *J* = 8.9 Hz, 2H), 6.9 (d, *J* = 8.5 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 6.18 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.89 (s, 2H), 4.31 (dd, *J* = 13.4, 3.0 Hz, 1H), 4.09 (dt, *J* = 13.3, 2.0 Hz, 1H), 3.64 (s, 3H), 3.41 (m, 2H), 2.89 (td, *J* = 12.8, 2.8 Hz, 1H), 2.82 (t, *J* = 11.6 Hz, 1H), 2.70 (td, *J* = 5.8 Hz, 1H), 2.05 (m, 1H), 1.73 (dd, *J* = 13.2, 3.1 Hz, 1H), 1.67 (qd, *J* = 12.1, 4.4 Hz, 1H). ^{13}C NMR (125 MHz DMSO-d_6 @ 100 °C): 160.5 (d, *J* = 242.6 Hz), 154.7, 153.6, 147.4, 141.0, 139.7 (d, *J* = 3.0 Hz), 128.6 (d, *J* = 8.1 Hz), 114.5 (d, *J* = 21.4 Hz), 107.3, 105.9, 100.4, 97.6, 69.0, 51.6, 46.4, 43.5, 42.9, 40.6, 32.9. IR (film): 3008, 2916, 1701, 1510, 1488, 1450, 1412, 1276, 1223, 1185, 1132, 1037, 937, 832, 765 cm^{-1}. HRMS: Calcd for $C_{21}H_{23}NO_5F$ [M+1] 388.1560, found 388.1561.



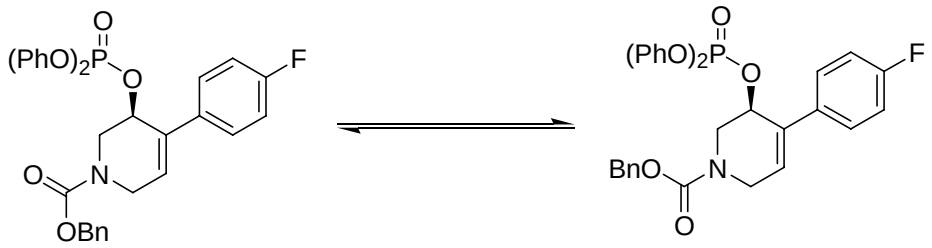
(-)-Paroxetine hydrochloride

To phenolic ether **2.43** (50 mg, 0.13 mmol, 100 mol%) was added KOH (94 mg, 1.68 mmol%, 1300 mol%), ethylene glycol (1.5 mL) and water (0.6 mL). The mixture was heated to 100 °C for 20h and then cooled to room temperature, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 X 5 mL), the combined organic layers were washed with water (2 X 5 mL), dried over $MgSO_4$, filtered, and evaporated in *vacuo* to give an oily residue. The residue was dissolved in ether (5 mL) and the resulting solution was treated with 4M HCl in dioxane (5mL), to give a white solid. The white solid was filtered, washed with ether and dried to afford paroxetine hydrochloride (45 mg, 0.123 mmol) 92% yield. Mp 132-134 °C, Lit[28i] 136-138 °C $[\alpha]_D^{23}$ – 85 ° (*c* = 1.0, CH_3OH), Lit[28i] -86.5 ° ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (dd, *J* = 8.2, 5.5 Hz, 2H), 7.00 (t, *J* = 8.5 Hz, 2H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.32 (d, *J* = 2.73 Hz, 1H), 6.10 (dd, *J* = 8.5, 2.4 Hz, 1H), 5.88 (s, 2H), 3.73 (dd, *J* = 21.5, 14.4 Hz, 2H), 3.60 (d, *J* = 8.2 Hz, 1H), 3.48 (dd, *J* = 9.9, 4.4 Hz, 1H), 3.17 (t, *J* = 10.9 Hz, 1H), 2.04 (m, 1H), 2.90 (t, *J* = 11.3 Hz, 1H), 2.64 (m, 1H), 2.38 (q, *J* = 13.3 Hz, 2H), 2.03 (d, *J* = 6.3 Hz, 1H). IR (film): 3401, 2925, 1605, 1510, 1224, 1185, 1037, 831 cm^{-1}.



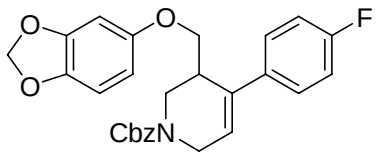
4-(4-Fluorophenyl)-3-hydroxy-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester 2.44

To a solution containing $CeCl_3 \bullet 7H_2O$ (1.09 g, 2.71 mmol, 100 mol%) and **2.33c** (0.88 g, 2.71 mmol, 100 mol%) in methanol (20 mL) was added $NaBH_4$ (0.102 g, 2.71 mmol, 100 mol%) in small portions over 2 minutes at room temperature. The mixture was allowed to stir for 5 minutes, after which water (30 mL) was added the reaction mixture was extracted with dichloromethane (3 X 20 mL), the organic extracts were then combined, dried over $MgSO_4$, filtered and concentrated in *vacuo* to afford an oily residue. Purification *via* column chromatography (SiO_2, 3:1 hexane/ethyl acetate) gives **2.44** (0.68 g, 2.08 mmol) in 76% yield as a white solid. Mp 106-108 °C, ^{1}H NMR (500 MHz, DMSO-d_6 @ 100 °C): δ 7.53 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.36 (m, 5H), 7.11 (t, *J* = 8.9 Hz, 2H), 6.09 (t, *J* = 3.5 Hz, 1H), 5.15 (s, 2H), 4.86 (t, *J* = 5.4 Hz , 1H), 4.49 (m, 1H), 4.29 (dd, *J* = 19.1, 3.7 Hz, 1H), 3.92 (dd, *J* = 13.2, 3.7 Hz, 1H), 3.89 (d, *J* = 16.5 Hz, 1H), 3.39 (dd, *J* = 13.2, 3.1 Hz, 1H). ^{13}C NMR (125 MHz DMSO-d_6 @ 100 °C): δ 161.0 (d, *J* = 244.1 Hz), 154.5, 136.6, 136.4, 135.2 (d, *J* = 3.05 Hz), 127.8, 127.2 (d, *J* = 7.6 Hz), 127.1, 126.9, 122.6, 114.2 (d, *J* = 21.4 Hz), 71.6, 63.0, 47.9, 43.0. IR (filml): 3414, 3033, 2915, 1691, 1510, 1432, 1360, 1229, 1125, 1070, 819, 698 cm^{-1}. HRMS: Calculated for $C_{19}H_{19}NO_3F$ [M+1] 328.1349, found 328.1349.



3-(Diphenoxyphosphoryloxy)-4-(4-fluorophenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester 2.45

Chlorodiphenylphosphate (0.5 ml, 2.31 mmol, 150 mol%), **2.44** (0.5 g, 1.54 mmol, 100 mol%), pyridine (0.25 mL, 3.08 mmol, 200 mol%) and DMAP (0.28 g, 2.31 mmol, 150 mol%) were reacted according to the procedure described for **2.39**. The crude product was purified *via* column chromatography (SiO_2, 9:1 to 4:1 dichloromethane/ethyl acetate) to give **2.45** (0.74 g, 1.32 mmol) in 86% yield as a white solid. Mp 59-61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (m, 17H), 6.91 (t, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 7.94 Hz, 2H), 6.20 (s, 1H), 5.62 (s, 1H), 5.2 (s, 1H), 4.60 (dd, *J* = 14.4, 3.0 Hz, 2H), 3.92 (d, *J* = 19.5 Hz, 1H), 3.76 (s, 1H), 3.52 (dd, *J* = 14.1, 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5 (d, *J* = 247.3 Hz), 155.3, 150.4, 150.0, 136.3, 133.4, 129.0 (d, *J* = 16.0 Hz), 128.4, 127.8, 127.7, 125.2, 125.0, 119.8, 115.4 (d, *J* = 21.4 Hz), 71.7, 67.4, 46.4, 43.6. IR (film): 3065, 2951, 1706, 1590, 1511, 1489, 1429, 1283, 1230, 1190, 1010, 957, 825, 766, 689 cm^{-1}. HRMS: Calcd for $C_{31}H_{28}NO_6FP$ [M+1] 560.163, found 560.1638.

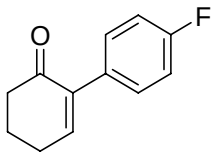


3-(Benzo[1,3]dioxol-5-yloxymethyl)-4-(4-fluorophenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester 2.46.

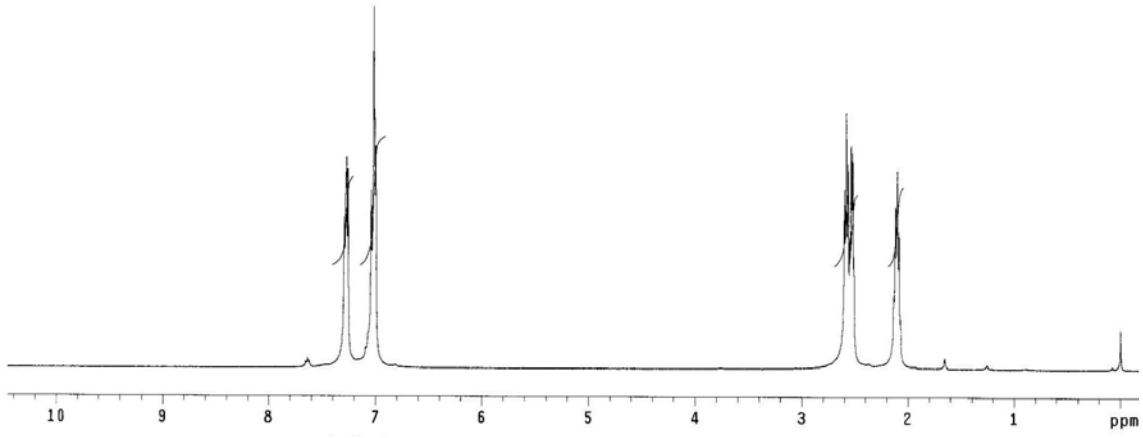
To a stirred solution of Ar-OCH_2SnBu_3 (240 mg, 0.54 mmol, 300 mol%) in THF (3 mL) at -78 °C was added *n*-BuLi (2.5 M in hexanes, 0.18 mL, 0.45 mmol, 250 mol%) dropwise. The reaction mixture was stirred at -78 °C for 1h at which point CuBr•SMe_2 (110 mg, 0.54 mmol, 300 mol%) in Me_2S (0.5 mL) was added dropwise. The reaction mixture was stirred an additional 30 minutes at -78 °C, at which **2.45** (100 mg, 0.18 mmol, 100 mol%) in THF (1 mL) was added. The reaction mixture continued to stir at -78 °C for an additional 1h period, at which point the reaction mixture was allowed to warm to -10 °C and 10% NH_4Cl aq (10 mL) was added. The aqueous layer was extracted with dichloromethane (3 x 5 mL), and the combined organic extracts were dried over $MgSO_4$, filtered and evaporated to afford an oily residue. Purification of the residue *via* column chromatography (SiO_2, 3:2 hexane:ethyl acetate) gives the title compound **2.46** (22 mg, 0.05 mmol) in 27% yield. ^{1}H NMR (500 MHz, DMSO-d_6 @ 100 °C): δ 7.45 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.29 (s, 5H), 7.13 (t, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.22 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.10 (t, *J* = 3.4 Hz, 1H), 5.89 (s, 2H), 5.08 (AB pattern *J* = 12.6 Hz, 2H), 4.33 (d, *J* = 13.3 Hz, 2H), 3.90 (d, *J* = 19.2, Hz, 1H), 3.72 (d, *J* = 5.1 Hz, 2H), 3.29 (d, *J* = 3.4 Hz, 2H), 3.20 (s, 1H). ^{13}C NMR (125 MHz DMSO-d_6 @ 100 °C): 161.2 (d, *J* = 244.6 Hz), 154.5, 153.5, 147.4, 141.0, 136.5, 135.4,

134.1, 127.7, 127.1, 127.1 (d, J = 8.1 Hz), 126.8, 123.2, 114.6 (d, J = 21.4 Hz), 107.3, 106.0, 100.4, 97.7, 68.1, 65.8, 43.1, 41.8, 36.9. IR (NaCl): 3033, 2962, 2877, 1701, 1602, 1508, 1465, 1431, 1260, 1224, 1184, 1129, 1037, 814 cm^{-1}. HRMS: Calcd for $C_{27}H_{25}NO_5F$ [M+1] 462.1717, found 462.1711.

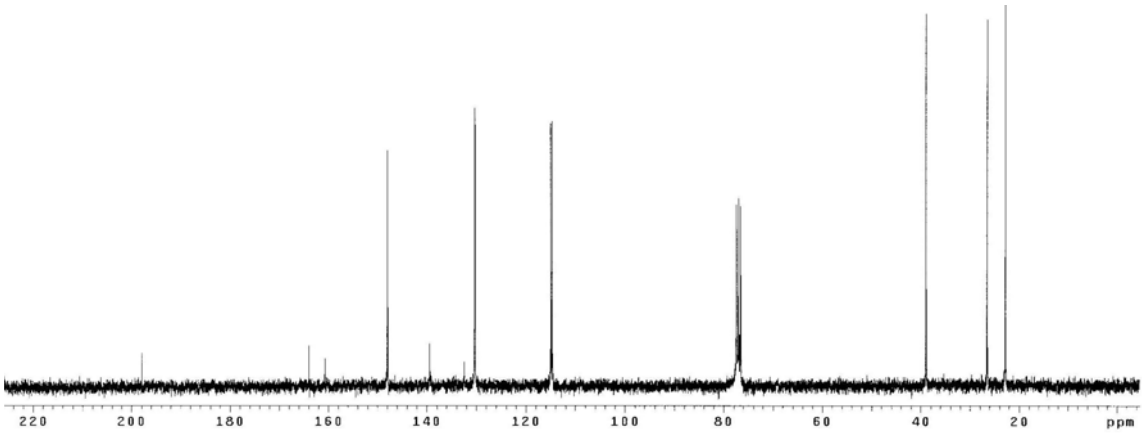
2.7 Spectroscopic Characterization Data



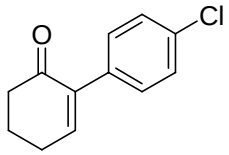
2-(4-Fluorophenyl)cyclohex-2-enone 2.17c. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.02 (m, 3H), 2.58 (t, *J* = 6.5 Hz, 2H), 2.53 (q, *J* = 5.5 Hz, 2H), 2.10 (quint, *J* = 6.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 162.3 (d, *J* = 246.0 Hz), 147.9, 139.3, 132.4, 130.2 (d, 7.7 Hz), 114.8 (d, *J* = 21.5 Hz), 38.9, 26.5, 22.8. FTIR (NaCl): 3038, 2929, 1672, 1503, 1350, 1214, 1159 cm^{-1}. HRMS: calcd for $C_{12}H_{12}OF$ [M+1] 191.0872 found 191.0872.



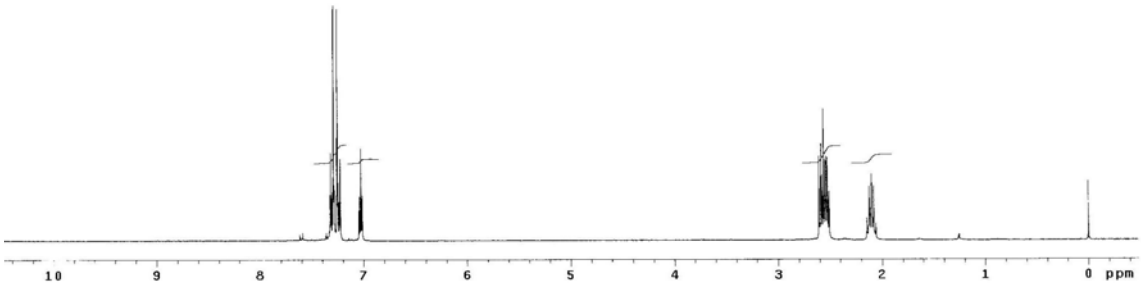
^{1}H NMR of **2.17c**



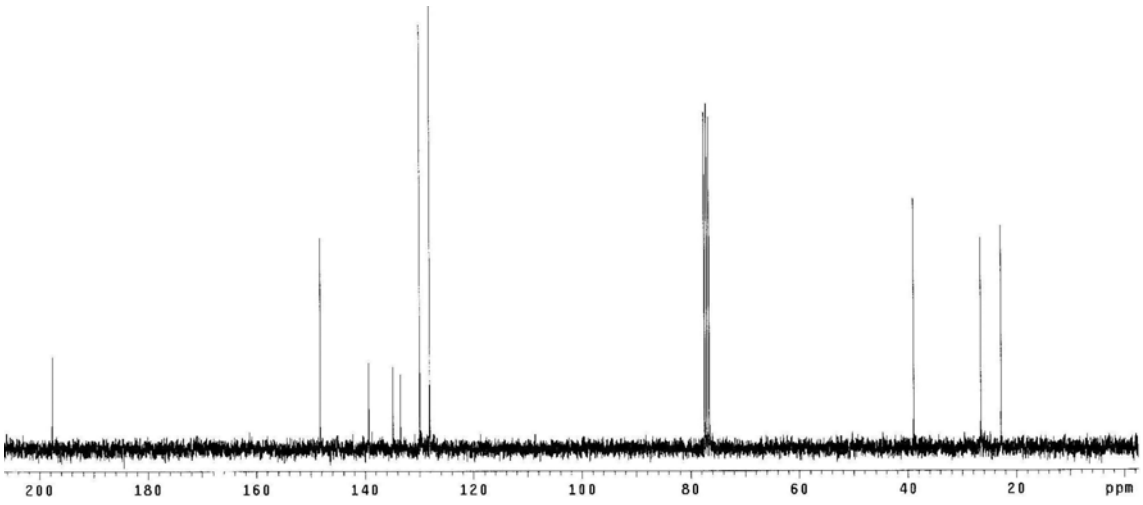
^{13}C NMR of **2.17c**



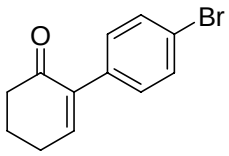
2-(4-Chlorophenyl)cyclohex-2-enone 2.17d. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31(A part of AB pattern, *J* = 8.7 Hz, 2H), 7.24 (B part of AB pattern, *J* = 8.7 Hz, 2H), 7.03 (t, *J* = 8.7 Hz, 1H), 2.56 (m, 4H), 2.10 (q, *J* = 6.2 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 197.6, 148.2, 139.3, 134.9, 133.5, 129.9, 128.1, 38.9, 26.5, 22.8. FTIR (NaCl): 2940, 2858, 1673, 1482, 1345, 1099, 826, cm^{-1}. HRMS: calcd for $C_{12}H_{12}OCl$ [M+1] 207.0576 found 207.0582.



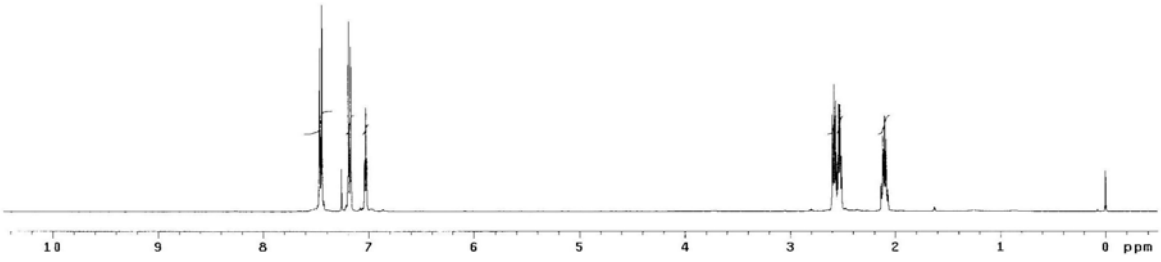
^{1}H NMR of **2.17d**



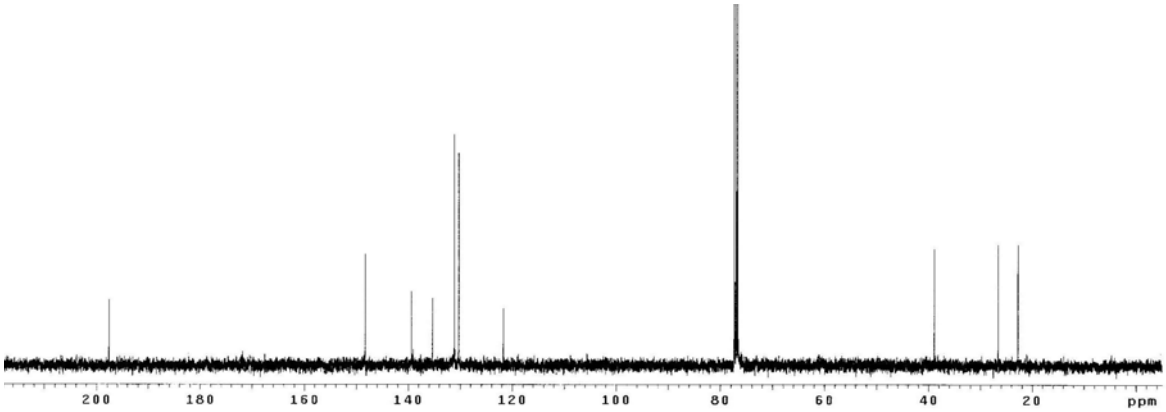
^{13}C NMR of **2.17d**



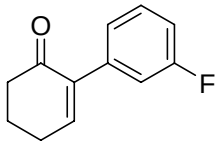
2-(4-Chlorophenyl)cyclohex-2-enone 2.17e. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (A part of AB pattern, *J* = 8.5 Hz, 2H), 7.18 (B part of AB pattern *J* = 8.5 Hz, 2H), 7.03 (t, *J* = 4.4 Hz, 1H) , 2.58 (t, *J* = 6.5 Hz, 2H), 2.53 (q, *J* = 5.8 Hz, 2H), 2.10 (quint, *J* = 6.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 148.3, 139.3, 135.3, 131.1, 130.3, 121.7, 38.9, 26.5, 22.9. FTIR (NaCl): 2945, 2869, 1667, 1481, 913, 732, 645 cm^{-1}. HRMS: calcd for $C_{12}H_{12}OBr$ [M+1] 251.0071 found 251.0078.



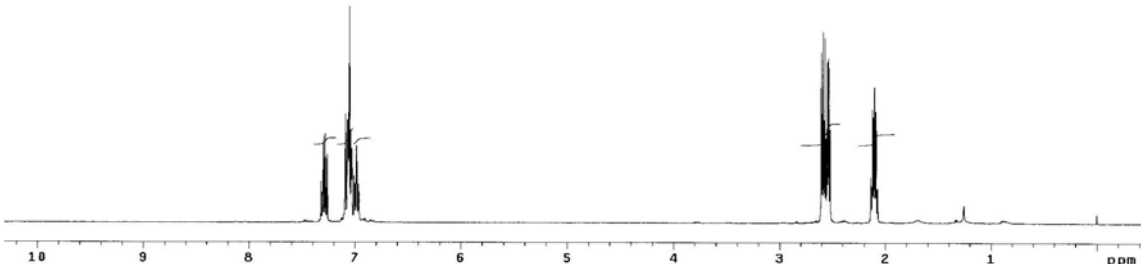
^{1}H NMR of **2.17e**



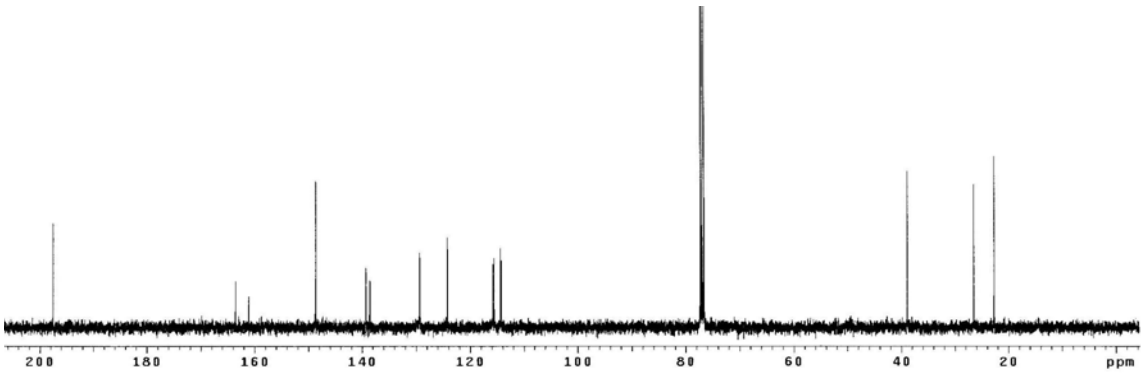
^{13}C NMR of **2.17e**



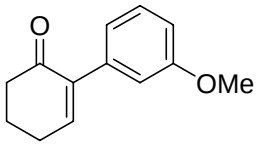
2-(3-Fluorophenyl)cyclohex-2-enone 2.17f. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 1H), 7.06 (m, 3H), 6.98 (td, *J* = 10.3, 1.0 Hz, 1H), 2.56 (m, 4H), 2.10 (quint, *J* = 6.16 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 162.4 (d, *J* = 245.23 Hz), 148.7, 139.2, 138.5 (d, *J* = 7.69 Hz), 129.4 (d, 8.45 Hz), 124.2, 115.5 (d, *J* = 21.50 Hz), 114.2 (d, *J* = 21.53 Hz), 38.9, 26.5, 22.7. FTIR (NaCl): 3055, 2940, 2863, 1667, 1585, 1471, 1422, 1214, 1164, 771 cm^{-1}. HRMS: calcd for $C_{12}H_{12}OF$ [M+1] 191.0872 found 191.0869.



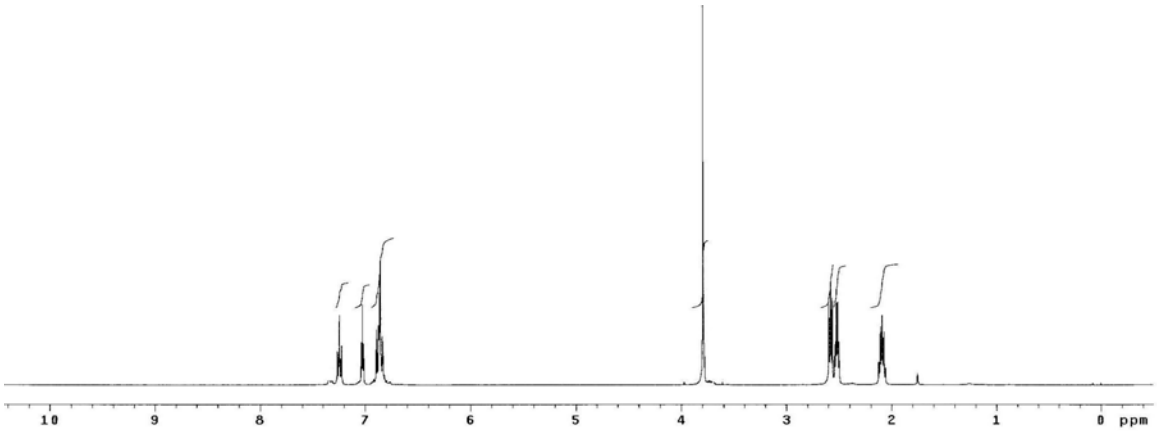
^{1}H NMR of **2.17f**



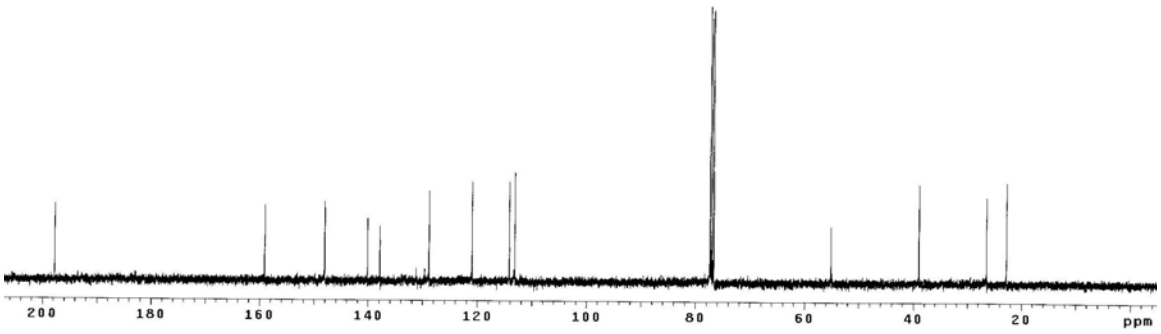
^{13}C NMR of **2.17f**



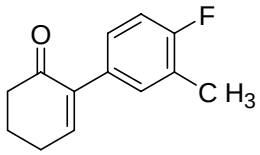
2-(3-Methoxyphenyl)cyclohex-2-enone 2.17g. ^{1}H NMR (300 MHz, $CDCl_3$): 7.24 (t, *J* = 8.2 Hz, 1H), 7.02 (t, *J* = 8.5 Hz, 1H), 6.86 (m, 3H), 3.79 (s, 3H), 2.57 (t, *J* = 6.5 Hz, 2H), 2.52 (q, *J* = 5.8 Hz, 2H), 2.09 (quint, *J* = 6.2 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 197.8, 159.1, 148.1, 140.1, 137.8, 128.9, 121.0, 114.1, 113.1, 55.1, 39.0, 26.5, 22.8. FTIR (NaCl): 3011, 2836, 1667, 1579, 1481, 1356, 1290, 1050, 782, 689 cm^{-1}. HRMS: calcd for $C_{13}H_{15}O_2$ [M+1] 203.1072 found 203.1070.



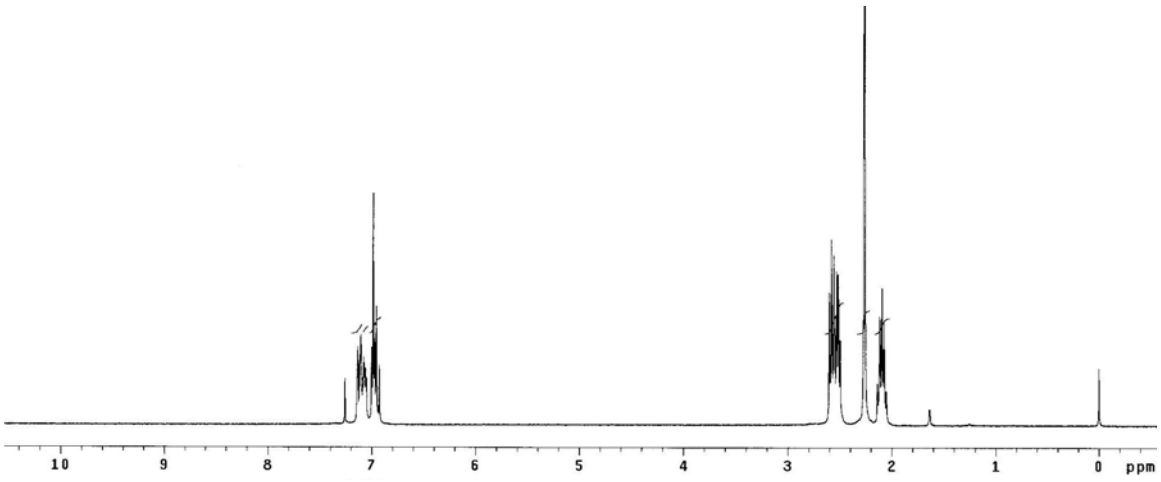
^{1}H NMR of **2.17g**



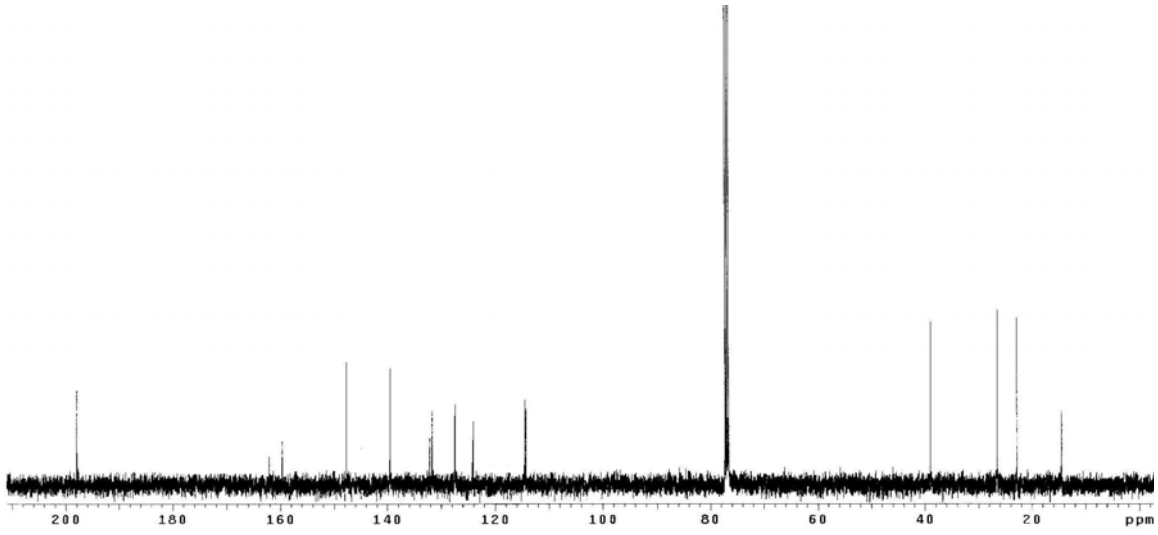
^{13}C NMR of **2.17g**



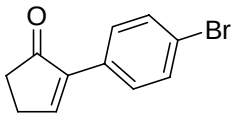
2-(4-Fluoro-3-methylphenyl)cyclohex-2-enone 2.17i. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 7.5 Hz, 1H), 7.08 (m, 1H), 6.96 (m, 2H), 2.57 (t, *J* = 6.5 Hz, 2H), 2.52 (q, *J* = 6.2 Hz, 2H), 2.26 (s, 3H), 2.09 (quint, *J* = 6.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 160.9 (d, *J* = 245.23 Hz), 147.7, 139.5, 132.2, 131.7 (d, *J* = 4.61 Hz), 127.5 (d, *J* = 8.46 Hz), 124.2 (d, *J* = 17.68 Hz), 114.5 (d, *J* = 22.29 Hz), 38.9, 26.5, 22.8, 14.5. FTIR (NaCl): 3049, 2929, 2864, 1673, 1498, 1345, 1236, 1121, 809 cm^{-1}. HRMS: calcd for $C_{13}H_{14}OF$ [M+1] 205.1028 found 205.1021.



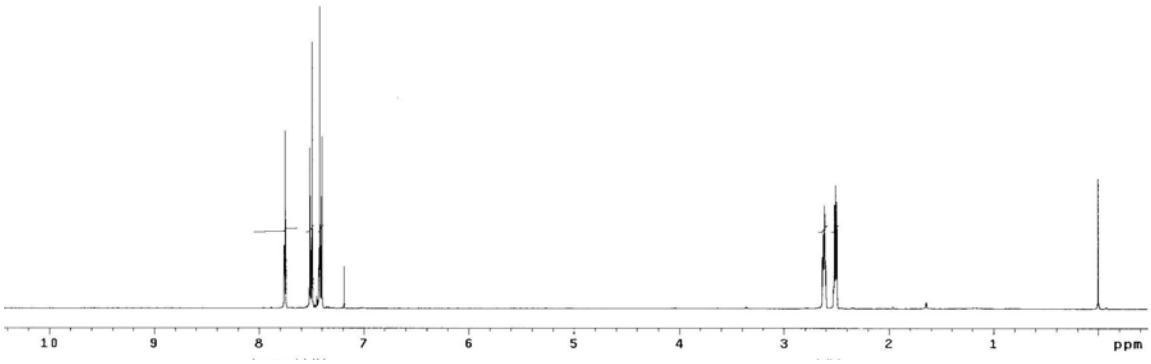
^{1}H NMR of **2.17i**



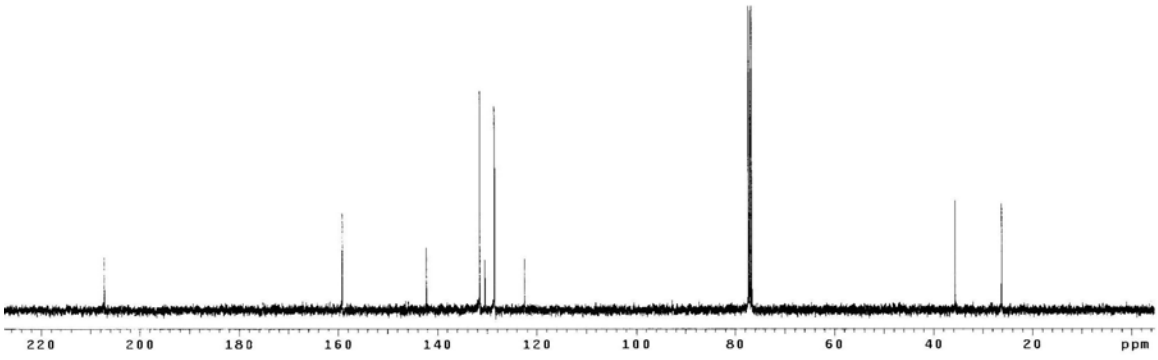
^{13}C NMR of **2.17i**



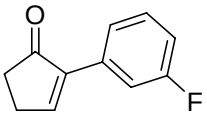
2-(4-Bromophenyl)cyclopent-2-enone 2.18e. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (t, *J* = 6.2 Hz, 1H), 7.51 (A part of AB pattern, *J* = 8.9 Hz, 2H), 7.42 (B part of AB pattern *J* = 8.9 Hz, 2H), 2.60 (m, 2H), 2.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.2, 159.2, 142.2, 131.5, 130.4, 128.5, 122.4, 35.6, 26.2. FTIR (NaCl): 3054, 2918, 1699, 1486, 907, 732 cm^{-1}. HRMS: calcd for $C_{11}H_{10}OBr$ [M+1] 136.9915 found 236.9914. MP 77-78 °C



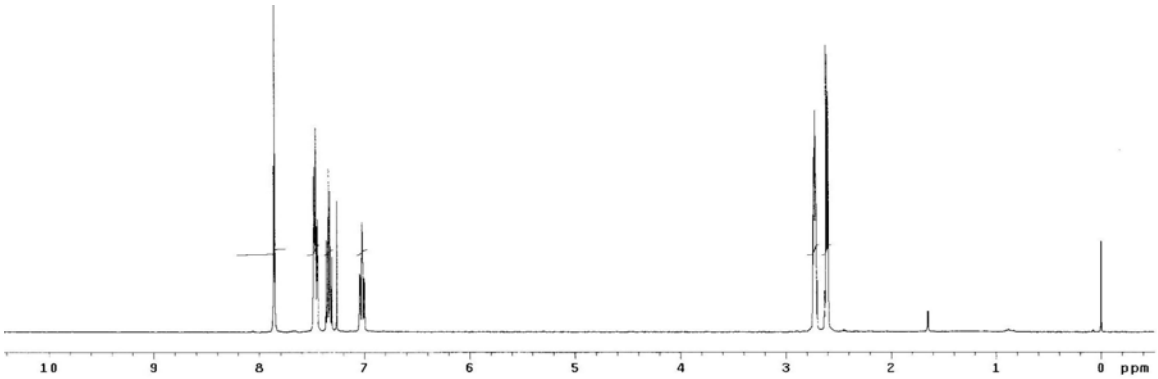
^{1}H NMR of **2.18e**



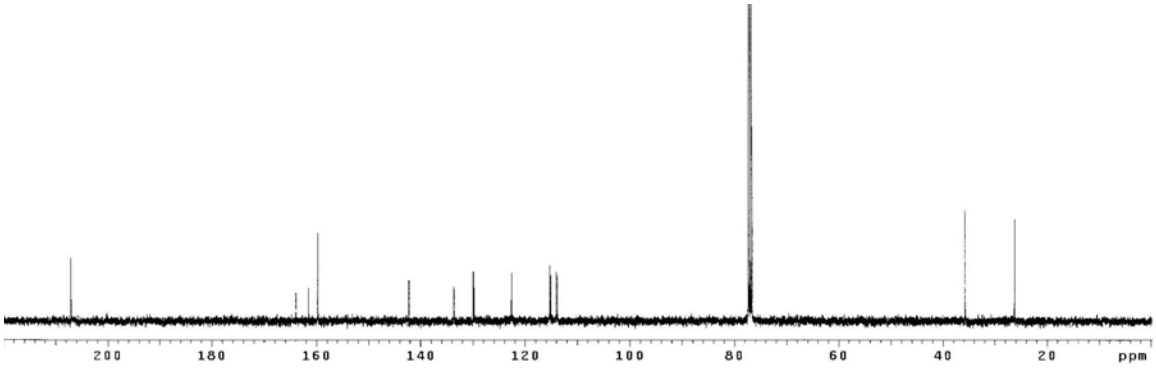
^{13}C NMR of **2.18e**



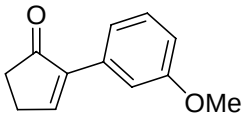
2-(3-Fluorophenyl)cyclopent-2-enone 2.18f. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (t, *J* = 3.1 Hz, 1H), 7.46 (m, 2H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.02 (t, *J* = 8.2 Hz, 1H), 2.72 (m, 2H), 2.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.1, 162.7, (d, *J* = 245.2 Hz), 159.8, 142.2, 133.6 (d, *J* = 8.45 Hz), 129.9 (d, *J* = 8.46 Hz), 122.6, 115.1 (d, *J* = 21.5 Hz) 114.0 (d, *J* = 22.3 Hz), 35.7, 26.2. FTIR (NaCl): 3046, 2918, 1700, 1585, 1487, 1334, 1192 771 cm^{-1}. HRMS: calcd for $C_{11}H_{10}OF$ [M+1] 177.0715 found 177.0721.



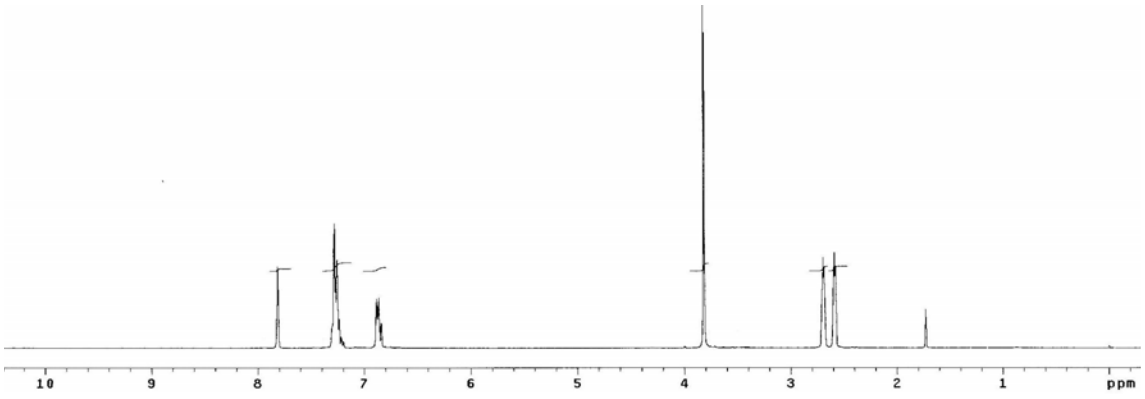
^{1}H NMR of **2.18f**



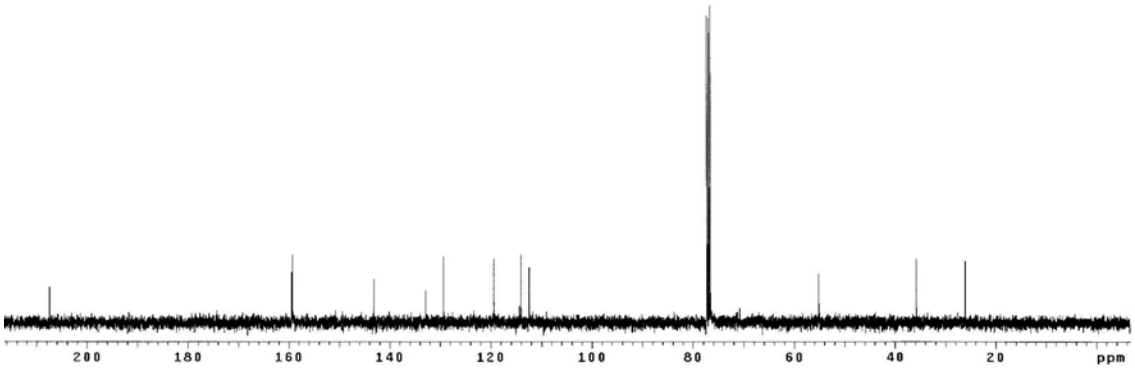
^{13}C NMR of **2.18f**



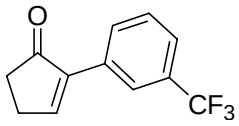
2-(3-Methoxyphenyl)cyclopent-2-enone 2.18g. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (t, *J* = 2.9 Hz, 1H), 7.22 (m, 3H), 6.87 (m, 1H), 3.83 (s, 3H), 2.70 (m, 2H), 2.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ.207.4, 159.5, 143.1, 132.9, 129.3, 119.4, 114.0, 112.4, 55.2, 35.8, 26.1. FTIR (NaCl): 3065, 2929, 2830, 1694, 1579, 1481, 1333, 1235, 1044, 781 cm^{-1}. HRMS: calcd for $C_{12}H_{13}O_2$ [M+1] 189.0915 found 189.0913.



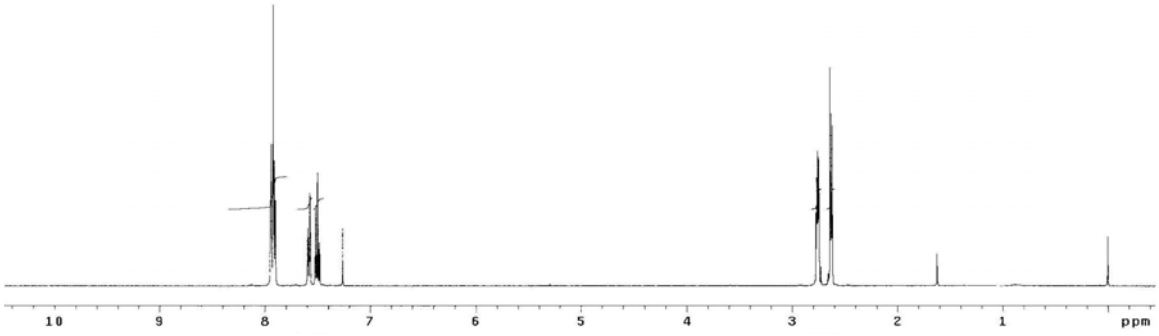
^{1}H NMR of **2.1g**



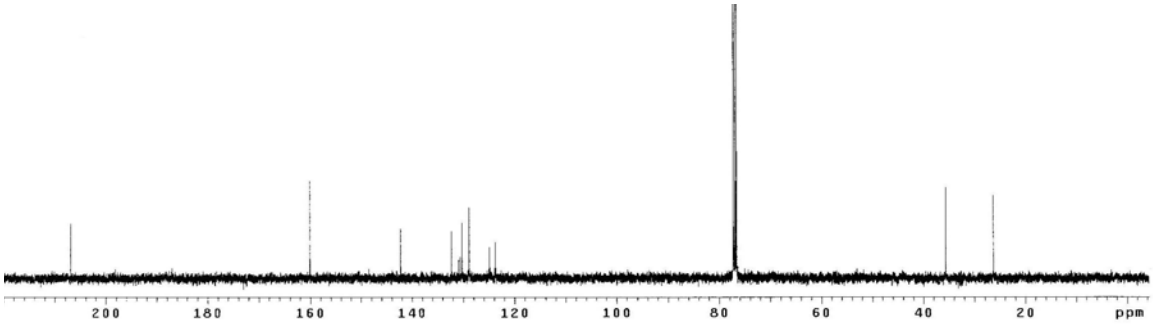
^{13}C NMR of **2.18g**



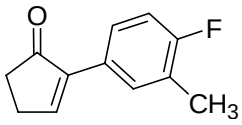
2-(3-Trifluoromethylphenyl)cyclopent-2-enone 2.18h. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (m, 2H), 7.52 (m, 3H), 2.74 (m, 2H), 2.62 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.9, 160.1, 142.2, 132.6, 131.2, 130.9, 130.5, 128.9, 125.0 (q, J = 3.8 Hz), 123.8 (q, J = 3.8 Hz), 35.6, 26.3. FTIR (NaCl): 3071, 2923, 2852, 1694, 1437, 1322, 1109, 1077 cm^{-1} . HRMS: calcd for $C_{12}H_{10}OF_3$ [M+1] 227.0683 found 227.0683.



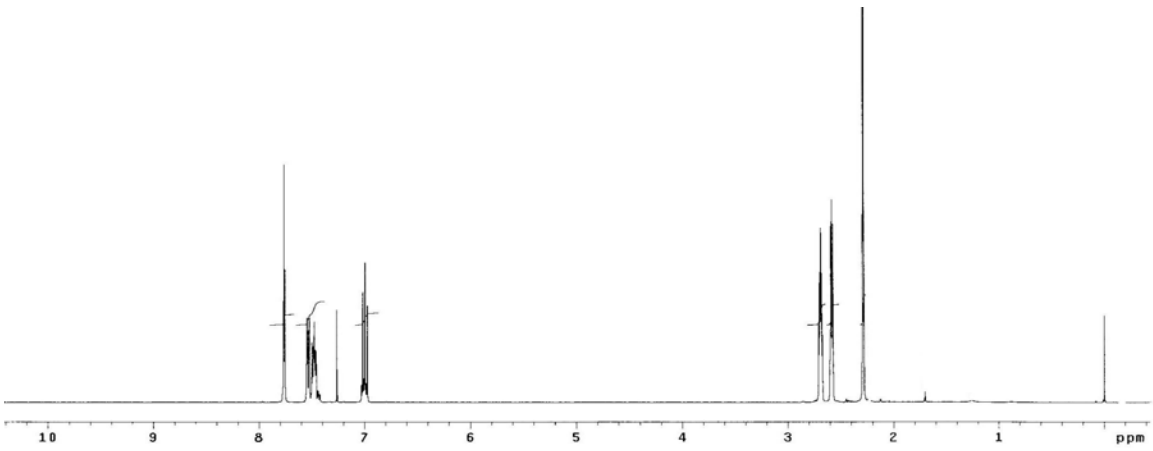
^{1}H NMR of **2.18h**



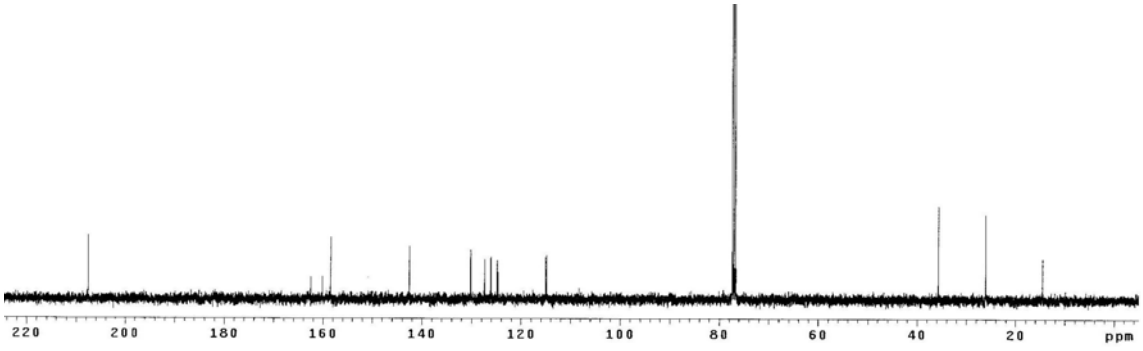
^{13}C NMR of **2.18h**



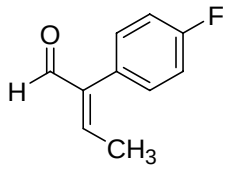
2-(4-Fluoro-3-methylphenyl)cyclopent-2-enone 2.18i. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (m, 1H), 7.53 (d, *J* = 1.7 Hz, 1H), 7.48 (m, 1H) 7.00 (t, *J* = 9.2 Hz, 1H), 2.69 (m, 2H), 2.59 (m, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.6, 161.3, (d, *J* = 246.7 Hz), 158.4, 142.5, 130.2, 127.4, 126.3, 124.7 (d, *J* = 17.68 Hz), 115.0 (d, *J* = 22.3 Hz), 35.7, 26.0, 14.6. FTIR (NaCl): 3076, 2912, 1683, 1503, 1312, 1229, 1109, 831, 781 cm^{-1}. HRMS: calcd for $C_{12}H_{12}OF$ [M+1] 191.0872 found 191.0875. M.P 66-68 °C.



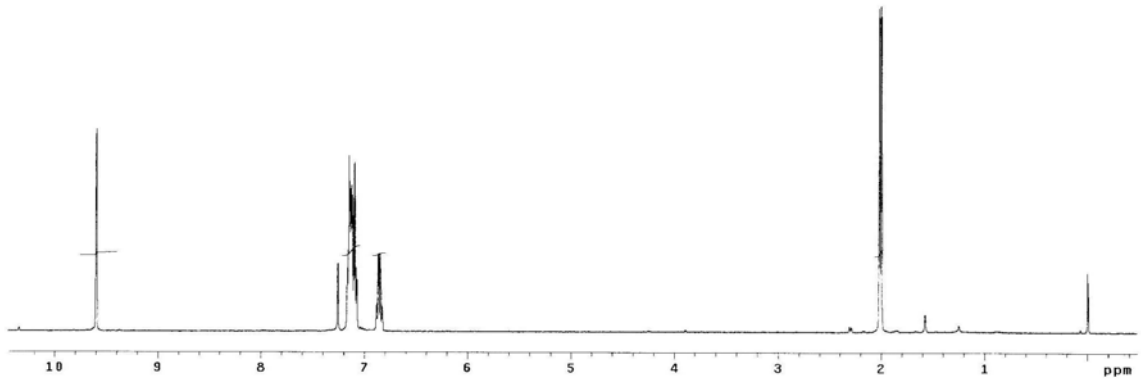
^{1}H NMR of **2.18i**



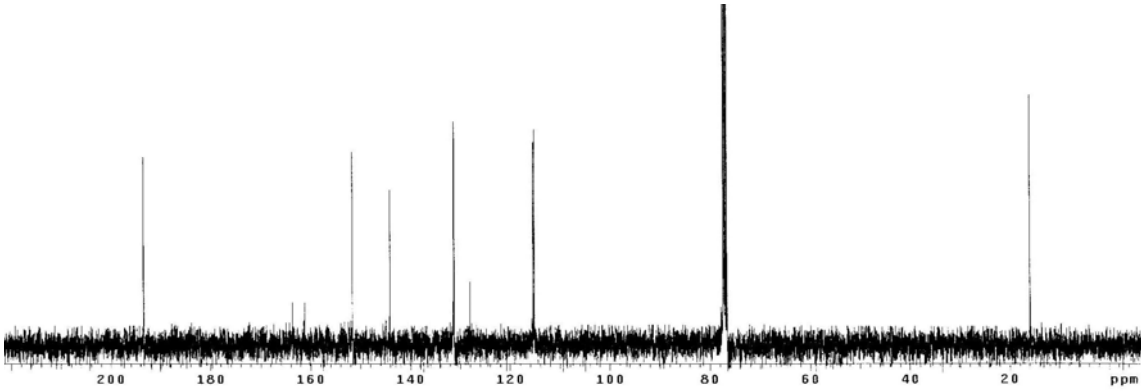
^{13}C NMR of **2.18i**



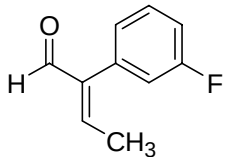
2-(4-Fluorophenyl)but-2-enal 2.19c. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.11 (m, 4H), 6.86 (q, *J* = 6.8 Hz, 1H), 2.01 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 162.4 (d, *J* = 247.5 Hz), 151.6, 144.1, 131.3 (d, *J* = 8.4 Hz), 128.0, 115.4 (d, *J* = 21.5 Hz), 15.9. FTIR (NaCl): 3059, 2830, 2704, 1694, 1508, 1224, 841, 732 cm^{-1}. HRMS: calcd for $C_{10}H_{10}OF$ [M+1] 165.0715 found 165.0716.



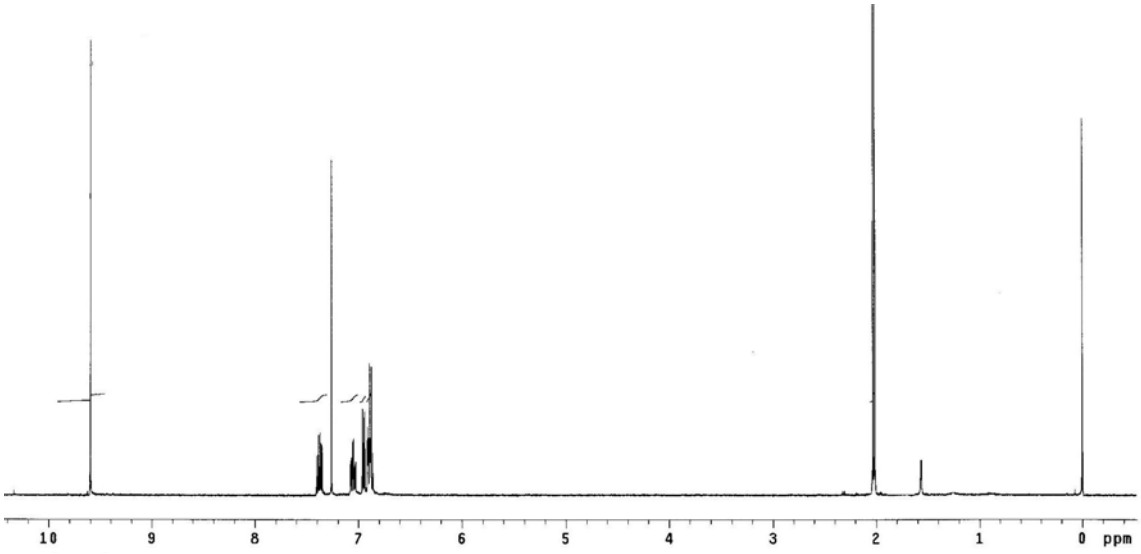
^{1}H NMR of **2.19c**



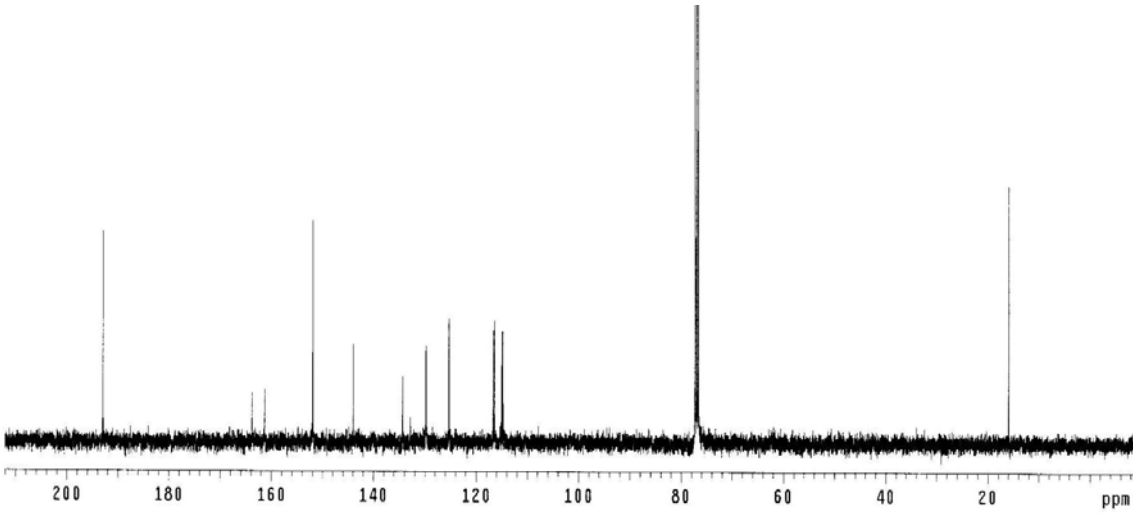
^{13}C NMR of **2.19c**



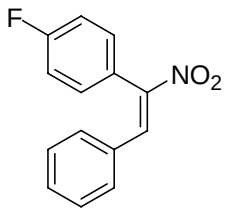
2-(4-Fluorophenyl)but-2-enal 2.19d. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.37 (q, *J* = 7.9 Hz, 1H), 7.05 (t, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 2.01 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 192.9, 162.5, (d, *J* = 246.8 Hz), 151.9, 143.9, 134.3 (d, *J* = 8.5 Hz), 129.9 (d, *J* = 8.5 Hz), 125.2, 116.5 (d, *J* = 21.5 Hz), 114.8 (d, *J* = 20.7 Hz), 15.9. FTIR (NaCl): 2825, 2716, 1694, 1574, 1432, 1246, 908, 738 cm^{-1}. HRMS: calcd for $C_{10}H_{10}OF$ [M+1] 165.0715 found 165.0721.



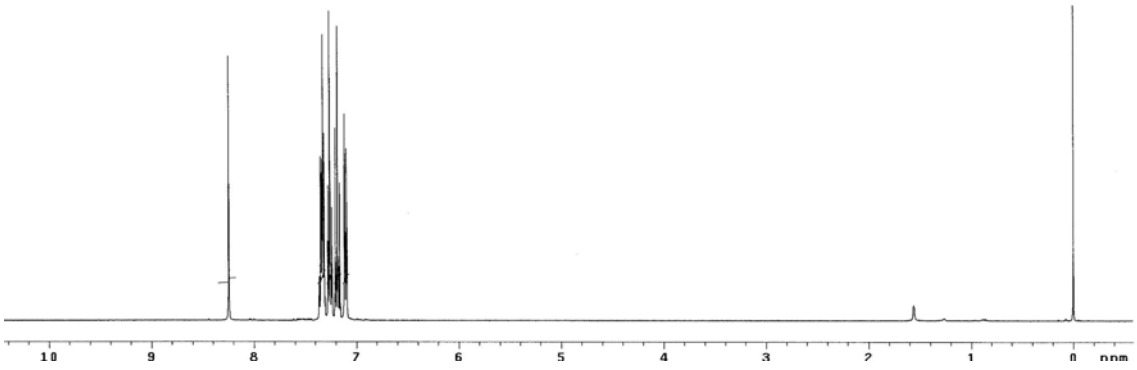
^{1}H NMR of **2.19d**



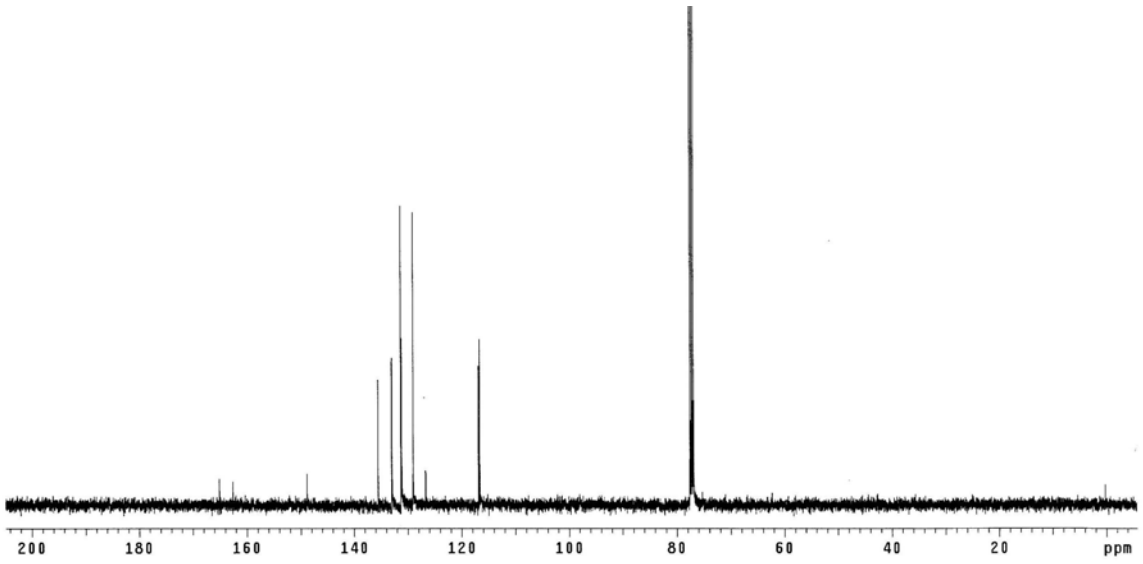
^{13}C NMR of **2.19d**



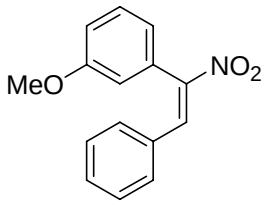
1-Fluoro-4-(1-nitro-2-phenylvinyl)benzene 2.20c. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.33 (m, 3H), 7.27 (t, *J* = 6.0 Hz, 2H), 7.20 (t, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8 (d, *J* = 251.3 Hz), 148.8, 135.5, 133.0 (d, *J* = 8.2 Hz), 131.3, 131.2, 131.1, 129.0, 126.7, 116.9 (d, *J* = 21.7 Hz). FTIR (NaCl): 3054, 1651, 1601, 1510, 1448, 1327, 1226, 1158, 971, 843, 765, 690 cm^{-1}. HRMS: calcd for $C_{14}H_{11}NO_2F$ [M+1] 244.0774 found 244.0772. MP 88–90 °C yellow solid.



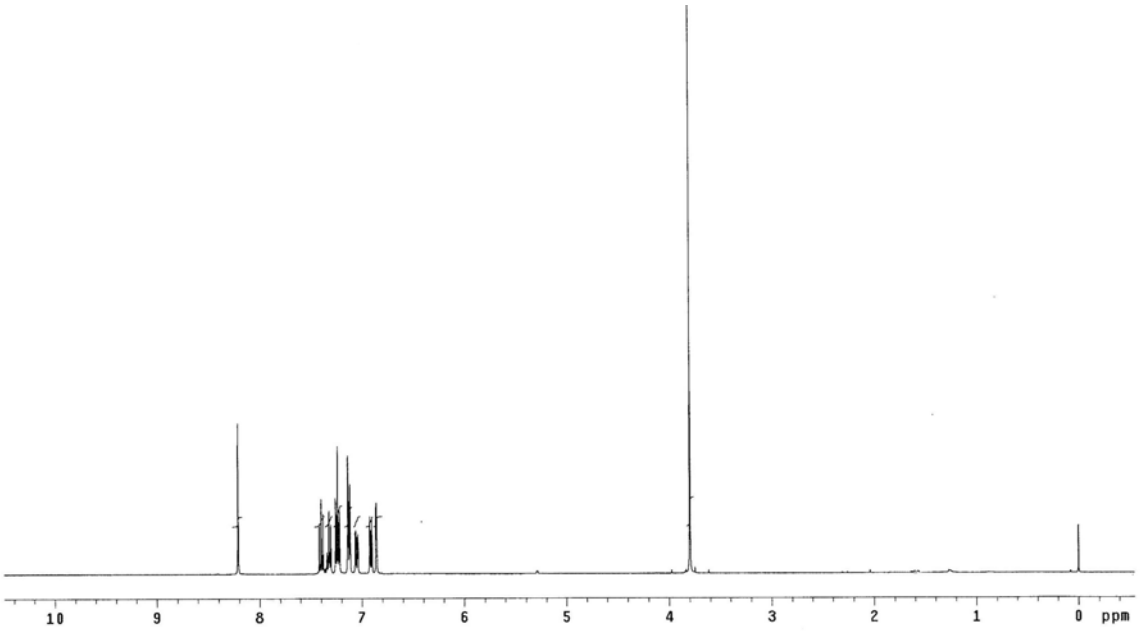
^{1}H NMR of **2.20c**



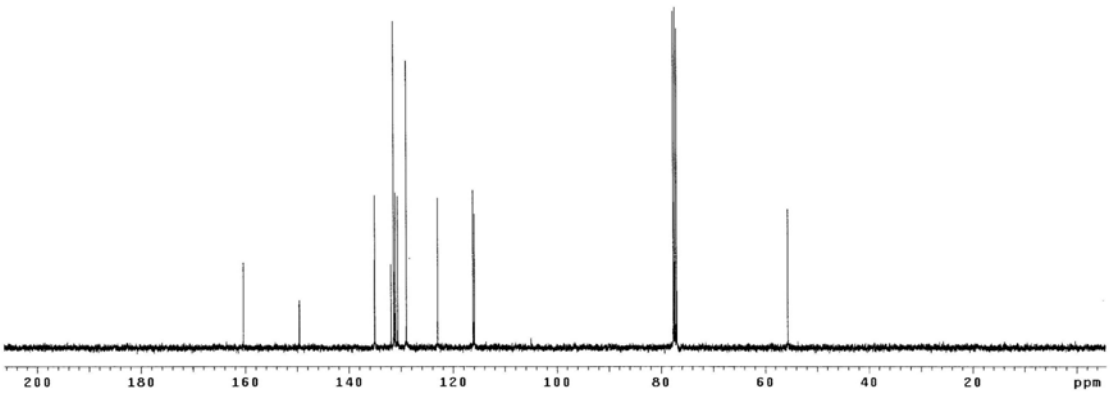
^{13}C NMR of **2.20c**



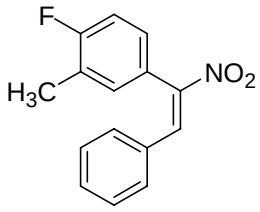
1-Methoxy-3-(1-nitro-2-phenylvinyl)benzene 2.20d. ^{1}H NMR (400 MHz $CDCl_3$): δ 8.21 (s, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 7.4 Hz, 2H), 7.05 (ddd, *J* = 1.0, 2.5, 5.9 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 7.86 (s, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 149.6, 135.0, 131.9, 131.4, 131.3, 131.1, 130.6, 129.0, 123.0, 116.2, 116.0, 55.6. FTIR (NaCl): 3055, 2911, 1646, 1514, 1448, 1316, 1244, 1113, 897, 753, 681 cm^{-1}. HRMS: calcd for $C_{15}H_{14}NO_3$ [M+1] 256.0974 found 256.0977.



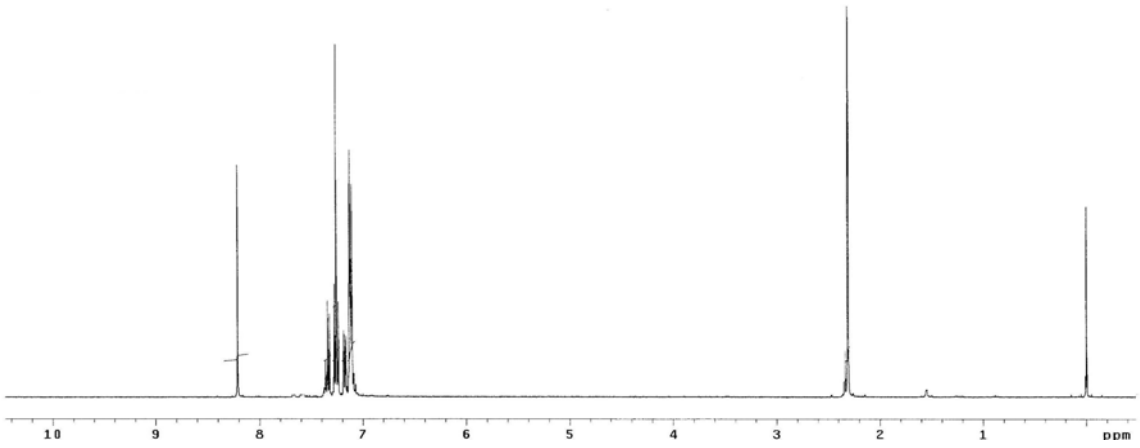
^{1}H NMR of **2.20d**



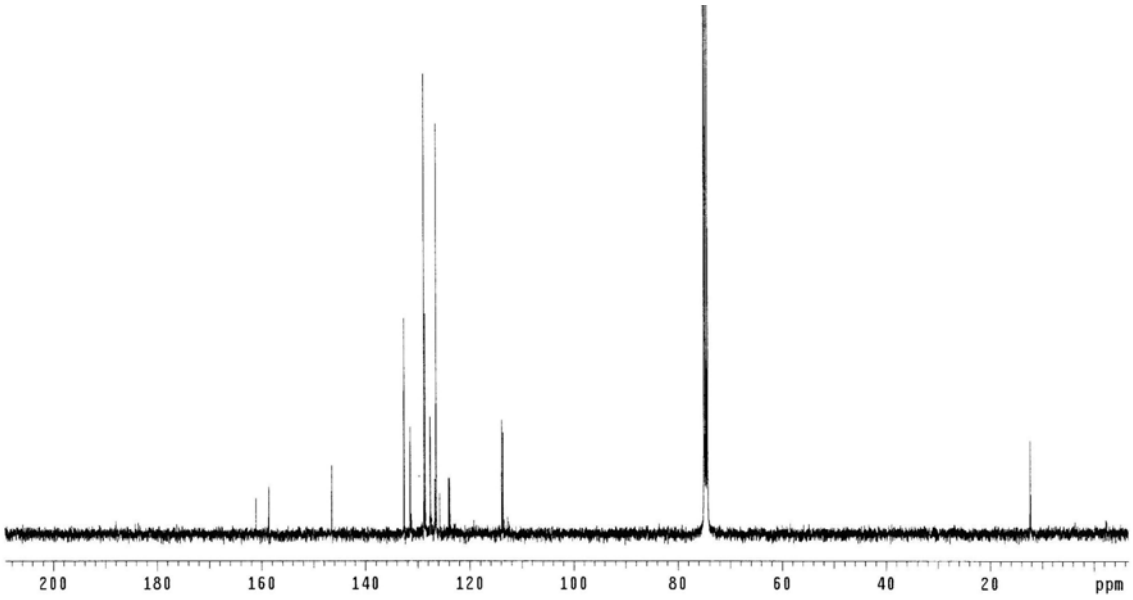
^{13}C NMR of **2.20d**



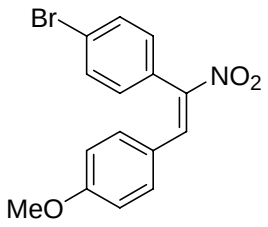
1-Fluoro-2-methyl-4-(1-nitro-2-phenylvinyl)benzene 2.20e. ^{1}H NMR (400 MHz $CDCl_3$): δ 8.21 (s, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.26 (t, *J* = 6.6 Hz, 2H), 7.17 (d, *J* = 6.6 Hz, 1H), 7.10 (m, 4H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (d, *J* = 250.0 Hz), 148.9, 134.9, 133.8, 133.7, 131.1, 130.9, 129.9 (d, *J* = 8.2 Hz), 128.8, 126.4, 126.2, 116.1 (d, *J* = 22.4 Hz), 14.6. FTIR (NaCl): 3048, 2931, 1652, 1593, 1521, 1449, 1372, 1324, 1243, 1200, 1118, 980, 905, 767, 690, 767, 690 cm^{-1}. HRMS: calcd [M+1] for $C_{15}H_{13}NO_2F$ 258.0930 found 258.0929. MP 85–86 °C pale yellow solid.



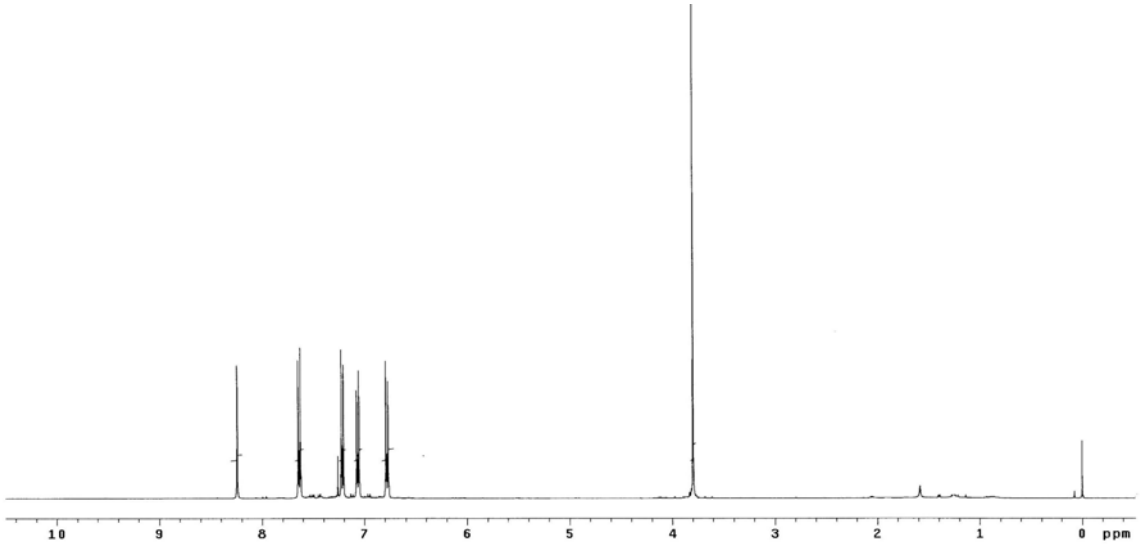
^{1}H NMR of **2.20e**



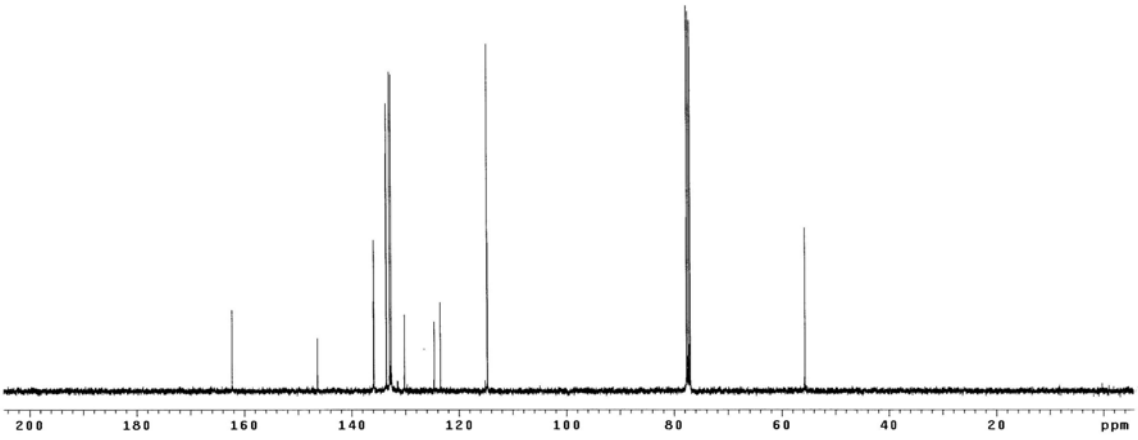
^{13}C NMR of **2.20e**



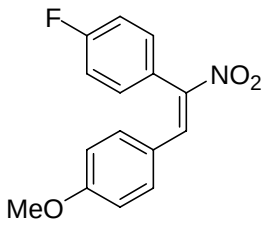
1-Bromo-4-[1-nitro-2 -(4-methoxyphenyl)vinyl]benzene 2.21b.^{1}H NMR (400 MHz $CDCl_3$): δ 8.24 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 146.4, 135.8, 133.5, 132.9, 132.6, 130.2, 124.6, 123.4, 114.7, 55.6. FTIR (NaCl): 3048, 2967, 1644, 1601, 1517, 1484, 1379, 1303, 1258, 1174, 1069, 971, 832, 801 cm^{-1}. HRMS calcd for $C_{15}H_{13}NO_3Br$ [M+1] 334.0079 found 334.0083. MP 130–131 °C yellow solid.



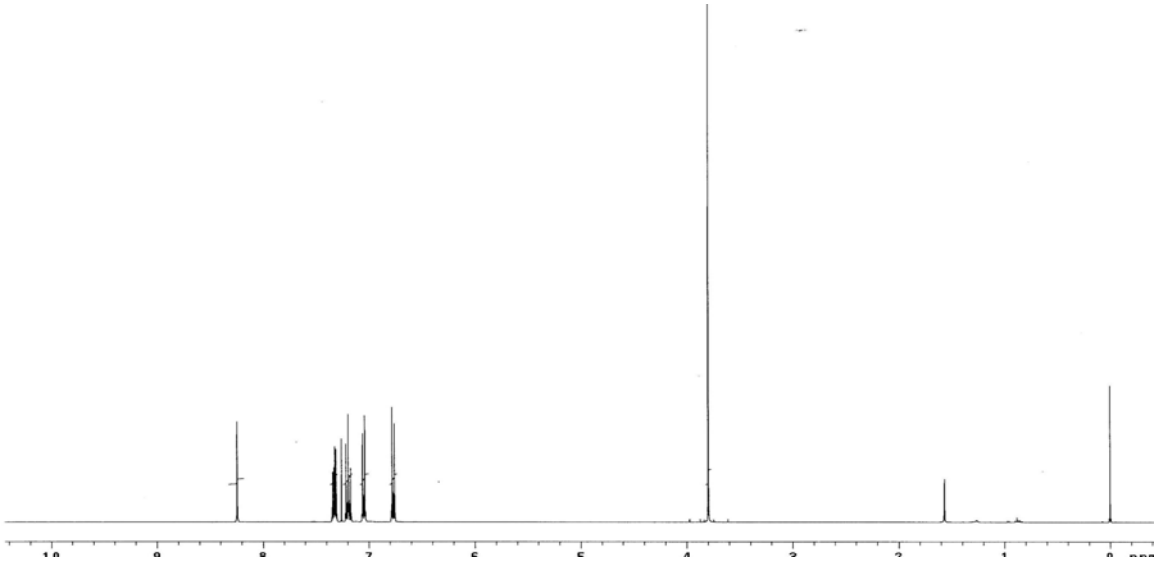
^{1}H NMR of **2.21b**



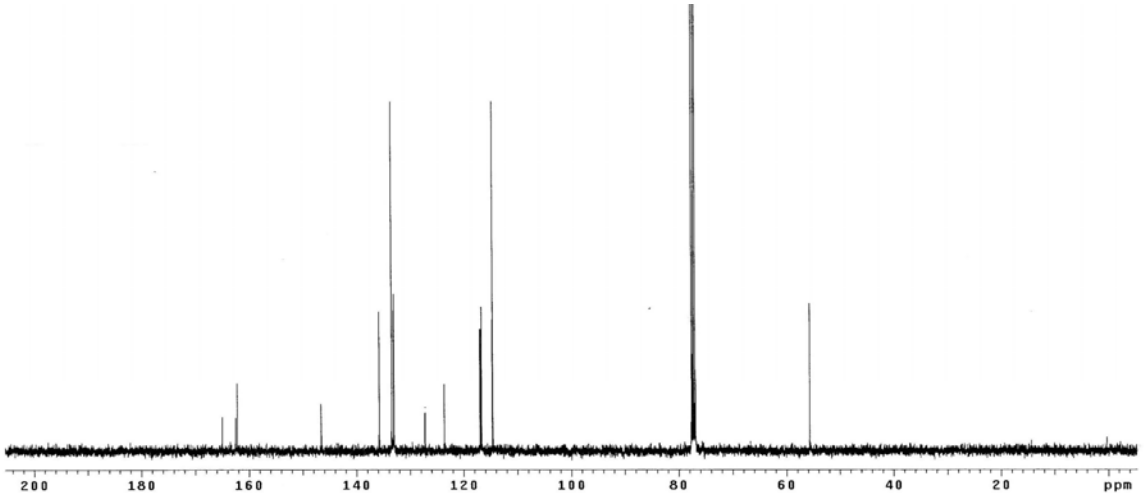
^{13}C NMR of **2.21b**



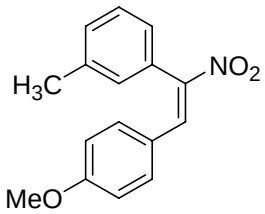
1-Fluoro-4-[1-nitro-2-(4-methoxyphenyl)vinyl]benzene 2.21c. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.32 (m, 2H), 7.20 (t, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7 (d, *J* = 250.6 Hz), 162.1, 146.5, 135.7, 133.4, 133.0 (d, *J* = 8.2 Hz), 127.3, 123.6, 116.8 (d, *J* = 21.7 Hz), 114.6, 55.6. FTIR (NaCl): 3072, 2935, 2839, 1645, 1601, 1517, 1461, 1304, 1259, 1223, 1176, 1207, 974, 833, 794 cm^{-1}. HRMS: calcd for $C_{15}H_{13}NO_3F$ [M+1] 274.0879 found 274.0879. MP 129–131°C yellow solid.



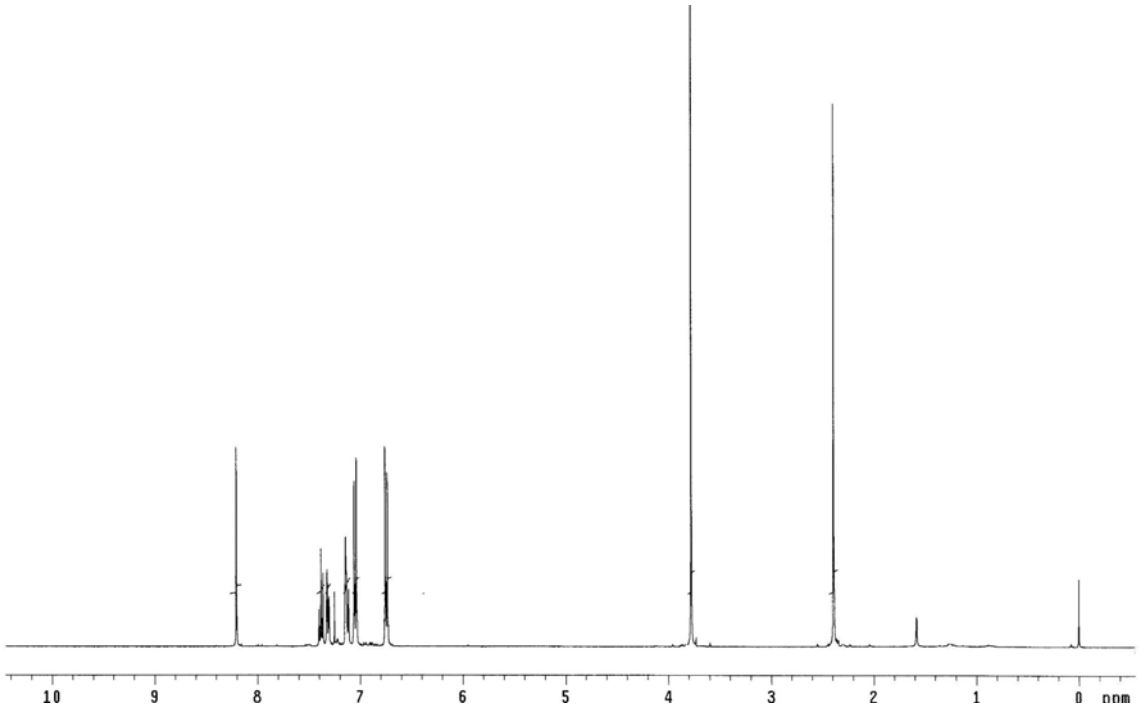
^{1}H NMR of **2.21c**



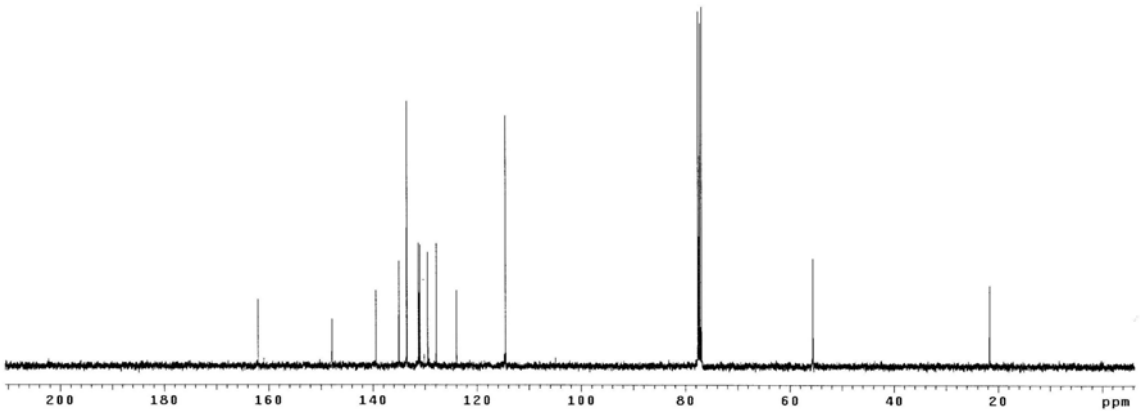
^{13}C NMR of **2.21c**



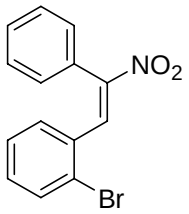
1-Fluoro-4-[1-nitro-2-(4-methoxyphenyl)vinyl]benzene 2.21d. ^{1}H NMR (400 MHz $CDCl_3$): δ 8.20 (s, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.13 (m, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 7.0Hz, 2H), 3.80 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 147.8, 139.4, 135.0, 133.5, 131.2, 131.1, 130.9, 129.4, 127.8, 123.9, 114.5, 55.6, 21.7. FTIR (NaCl): 3013, 2932, 2825, 1644, 1599, 1511, 1460, 1273, 1298, 1254, 1175, 1026, 880, 829, 784 cm^{-1}. HRMS: calcd for $C_{16}H_{16}NO_3$ [M+1] 270.1130 found 270.1133.



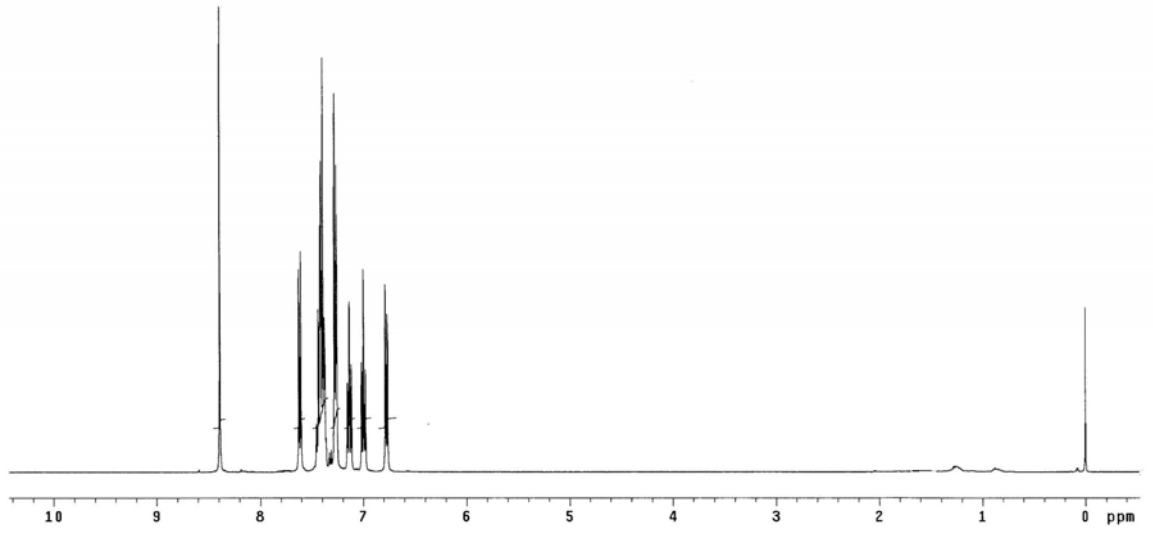
^{1}H NMR of **2.21d**



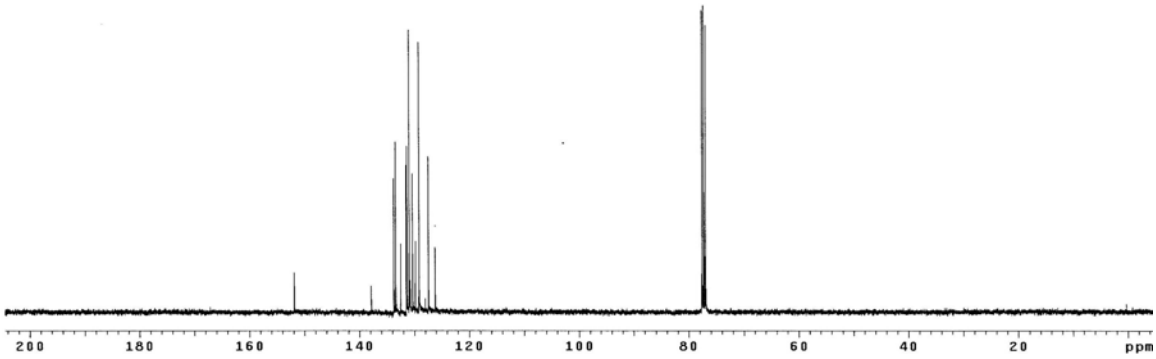
^{13}C NMR of **2.21d**



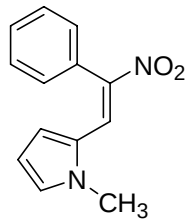
1-Bromo-2-(2-nitro-2-phenylvinyl)benzene 2.22b. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.42 (m, 3H), 7.27 (dd, *J* = 1.4, 8.0 Hz, 2H), 7.13 (td, *J* = 1.7, 7.8 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.76 (dd, *J* = 1.4, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 137.8, 133.7, 133.4, 132.5, 131.4, 131.3, 130.9, 130.7, 130.3, 129.8, 129.1, 127.4, 126.2. FTIR (NaCl): 3059, 1651, 1585, 1523, 1464, 1327, 1281, 1211, 1166, 1027, 971, 912, 863, 757, 699 cm^{-1}. HRMS: Calcd for $C_{14}H_{11}NO_2Br$ [M+1] 303.9973 found 303.9973. MP 92 – 93 °C pale yellow solid.



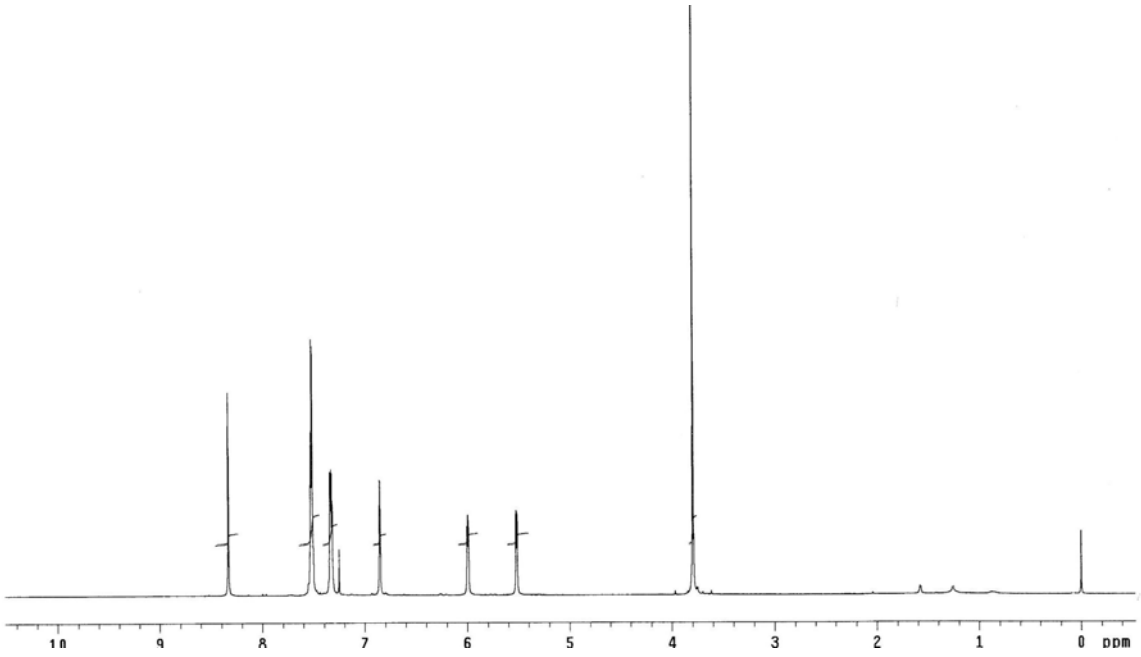
^{1}H NMR of **2.22b**



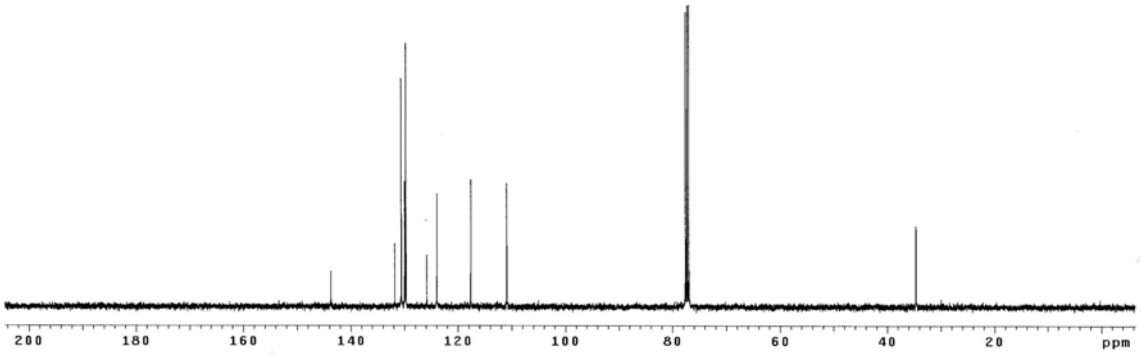
^{13}C NMR of **2.22b**



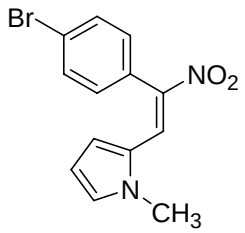
1-Methyl-2-(2-nitro-2-phenylvinyl)-1*H*-pyrrole 2.23b. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.51 (m, 3H), 7.33 (d, *J* = 4.1 Hz, 2H), 6.85 (s, 1H), 5.99 (t, *J* = 2.5Hz, 1H), 5.51 (d, *J* = 4.1Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 131.8, 130.5, 130.0, 129.7, 125.8, 123.9, 117.6, 110.9, 34.6. FTIR (NaCl): 3031, 1634, 1526, 1485, 1413, 1412, 1267, 1169, 1064, 978, 917, 740, 712, 654 cm^{-1}. HRMS: calcd for $C_{13}H_{13}N_2O_2$ [M+1] 229.0977 found 229.0978. MP 136-137 °C brown solid.



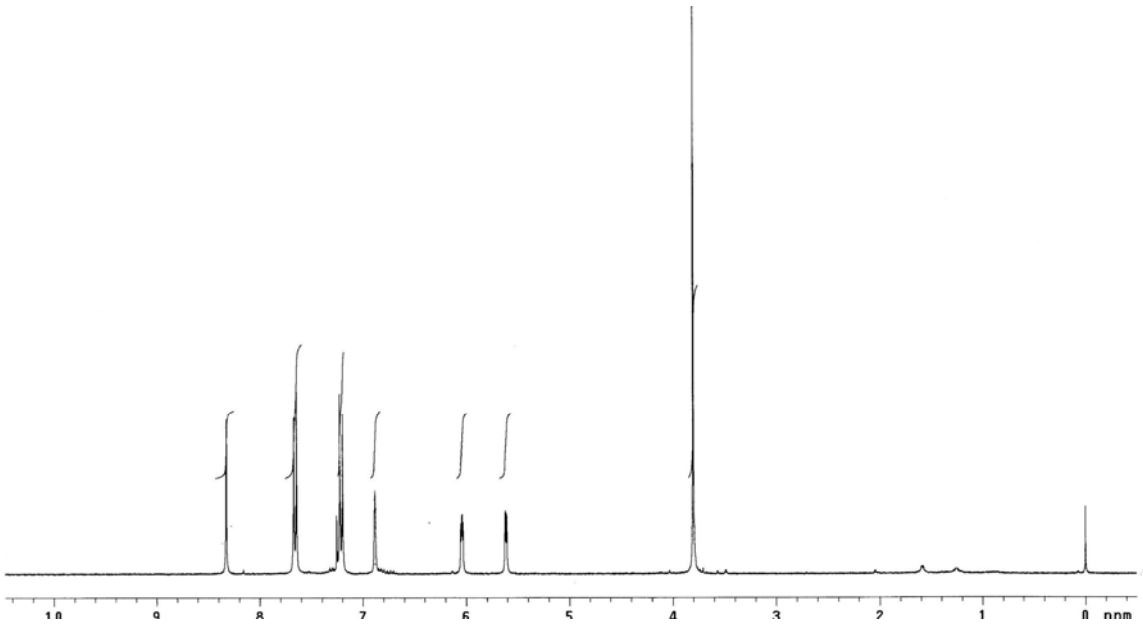
^{1}H NMR of **2.23b**



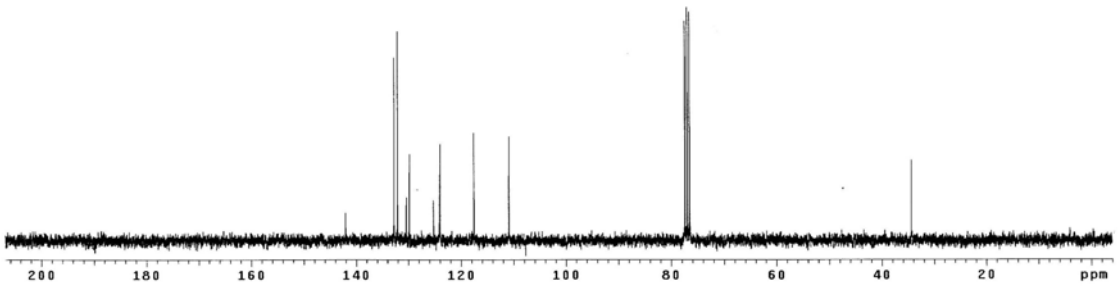
^{13}C NMR of **2.23b**



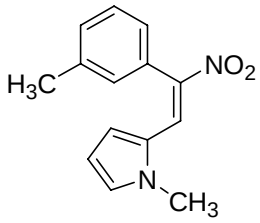
2-[2-(4-Bromophenyl)-2-nitrovinyl]-1-methyl-1*H*-pyrrole 2.23c. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.85 (s, 1H), 6.89 (s, 1H), 6.04 (t, *J* = 2.0 Hz, 1H), 5.61 (dd, *J* = 1.0, 4.3 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 132.8, 132.1, 130.4, 129.9, 125.2, 124.1, 124.0 117.5, 110.9, 34.4. FTIR (NaCl): 3048, 1629, 1586, 1505, 1443, 1290, 1243, 1180, 1060, 979, 924, 828, 772, 750 cm^{-1}. HRMS: calcd for $C_{13}H_{12}N_2O_2Br$ [M+1] 307.0082 found 307.0083. MP 201-202 °C brown solid.



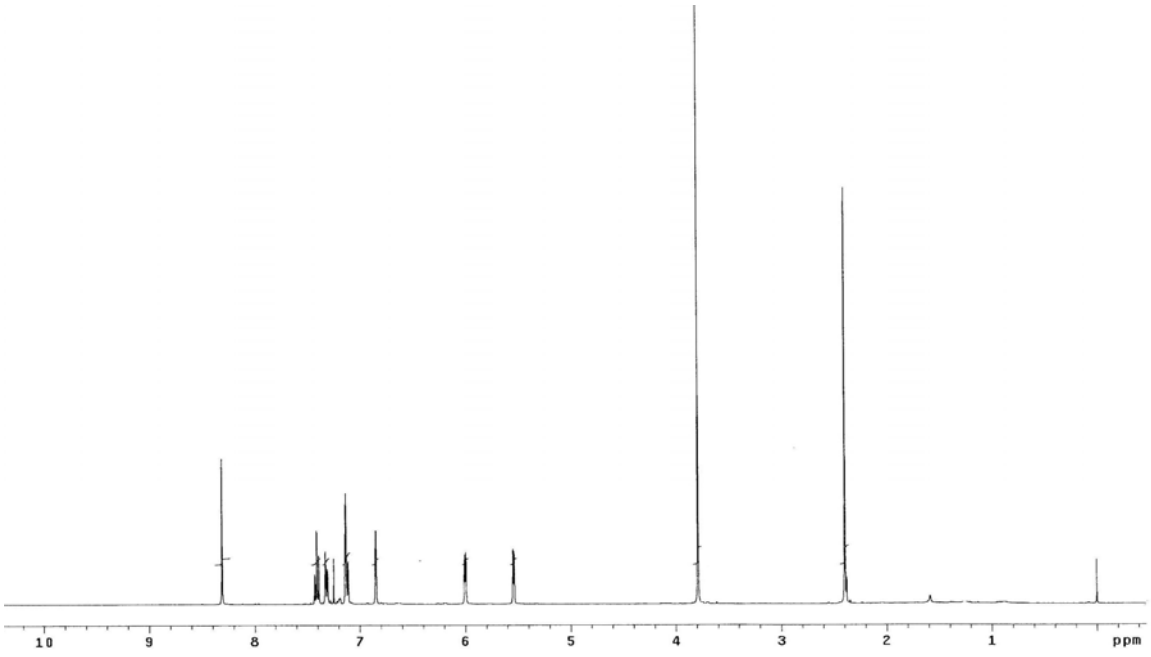
^{1}H NMR of **2.23c**



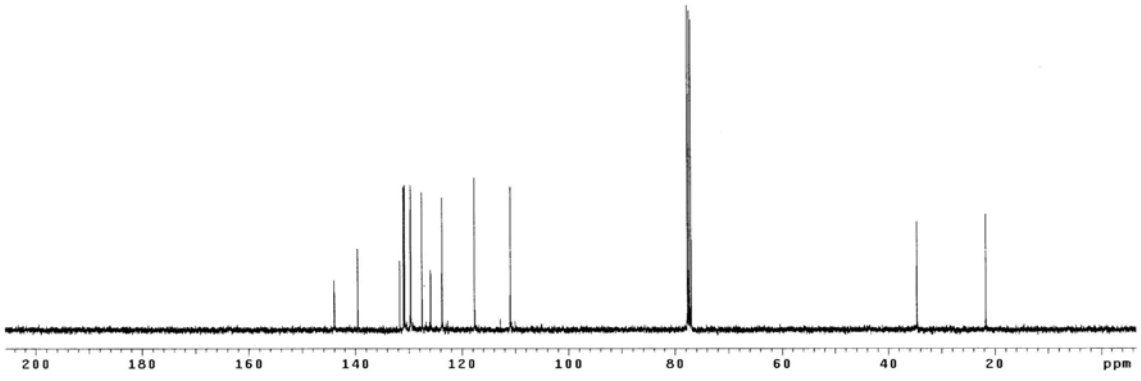
^{13}C NMR of **2.23c**



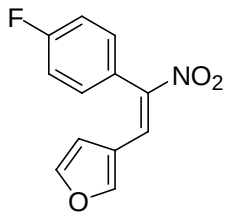
1-Methyl-2-(2-nitro-2-*m*-tolylvinyl)-1*H*-pyrrole 2.23d. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 3H), 6.85 (d, *J* = 2.1 Hz, 1H), 6.00 (dd, *J* = 2.4, 4.1 Hz, 1H), 5.54 (dd, *J* = 1.2, 4.1 Hz, 1H), 3.79 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 139.5, 131.7, 130.9, 130.8, 129.7, 129.6, 127.4, 125.9, 123.7, 117.6, 110.9, 34.6, 21.7. FTIR (NaCl): 3042, 1630, 1526, 1483, 1411, 1275, 1064, 1010, 747 cm^{-1}. HRMS: calcd for $C_{14}H_{15}N_2O_2$ [M+1] 243.1134 found 243.1134. MP 104-106 °C brownish yellow solid



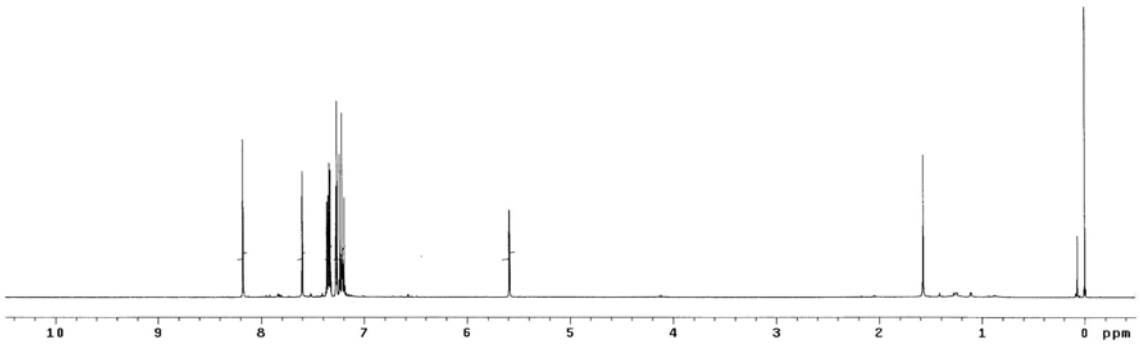
^{1}H NMR of **2.23d**



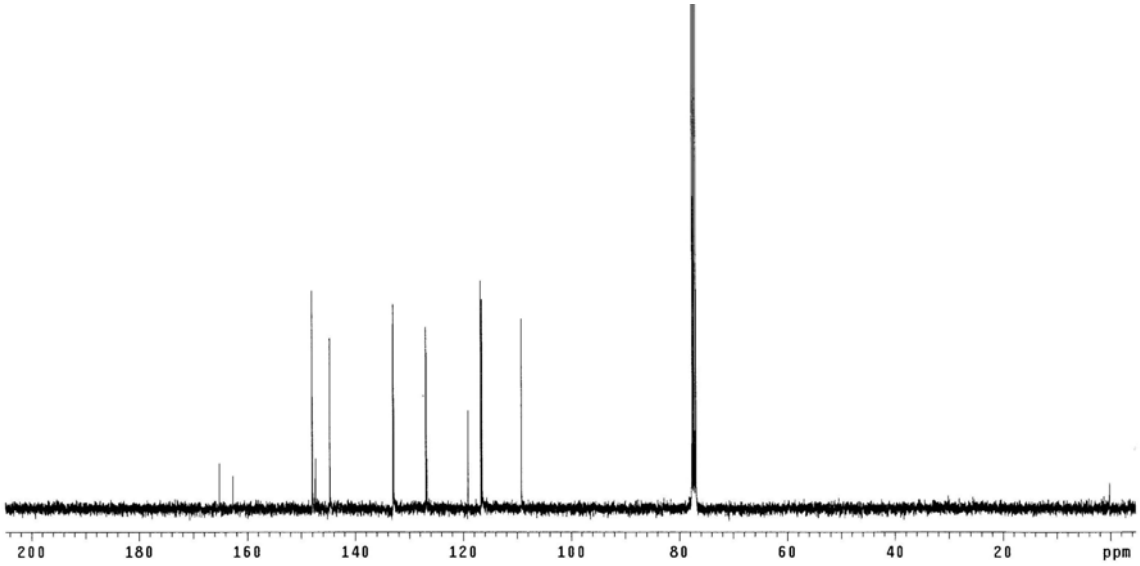
^{13}C NMR of **2.23d**



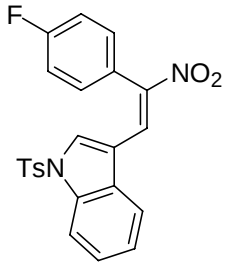
3-[2-(4-Fluorophenyl)-2-nitrovinyl]furan 2.24b. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.60 (s, 1H), 7.35 (d, *J* = 5.3 Hz, 1H), 7.33 (d, *J* = 5.3 Hz, 1H), 7.24 (td, *J* = 2.0, 0.6 Hz, 1H), 7.22 (t, *J* = 8.4Hz, 2H), 5.59 (d, *J* = 2Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8 (d, *J* = 251.3 Hz), 147.9, 147.4, 144.7, 133.0 (d, *J* = 8.2 Hz), 126.8 (d, *J* = 12.7Hz), 126.7, 119.1 116.6 (d, *J* = 21.7 Hz), 109.2. FTIR (NaCl): 3142, 3060, 2919, 1645, 1601, 1497, 1318, 1279, 1222, 1159, 1094, 1015, 977, 845, 750, 600, 563 cm^{-1}. HRMS: calcd for $C_{12}H_9NO_3F$ [M+1] 234.0566 found 234.0567. MP 96-98 °C brown solid



^{1}H NMR of **2.24b**

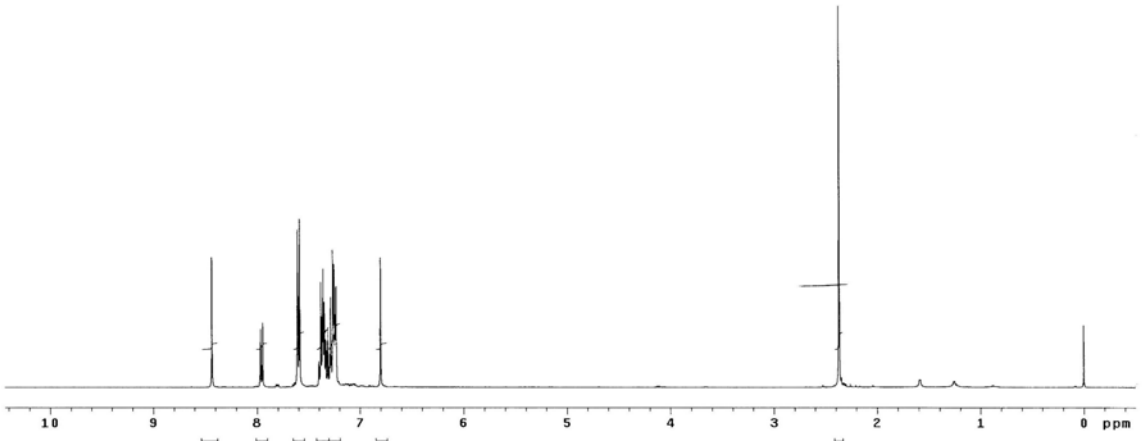


^{13}C NMR of **2.24b**

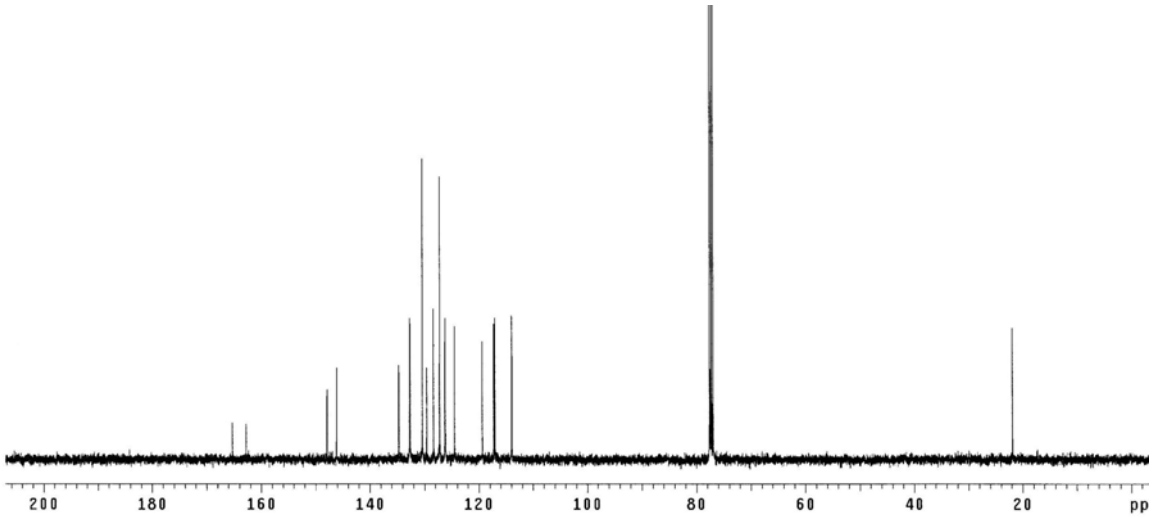


3-[2-(4-Fluorophenyl)-2-nitrovinyl]-1-(toluene-4-sulfonyl)-1H-indole 2.25b. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 3H), 7.35 (m, 4H), 7.25 (m, 4H), 6.8 (s, 1H), 3.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0 (d, *J* = 252.0, Hz), 147.9, 146.1, 134.7 (d, *J* = 3.0 Hz), 132.6 (d, *J* = 8.2 Hz), 130.4, 129.6, 128.3, 127.2, 126.2, 126.1, 124.4, 119.4, 117.1 (d, *J* = 21.7Hz), 113.9, 21.9. FTIR (NaCl): 3148, 2926, 1644, 1599, 1507, 1447, 1376, 1316, 1225, 1175, 1140, 1093,

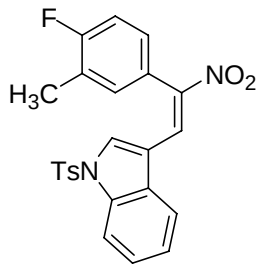
970, 812, 759, 669, 576 cm^{-1}. HRMS: calcd for $C_{23}H_{18}N_2O_4FS$ [M+1] 437.0971 found 437.0975. MP 141-142 °C yellow solid.



^{1}H NMR of **2.25b**

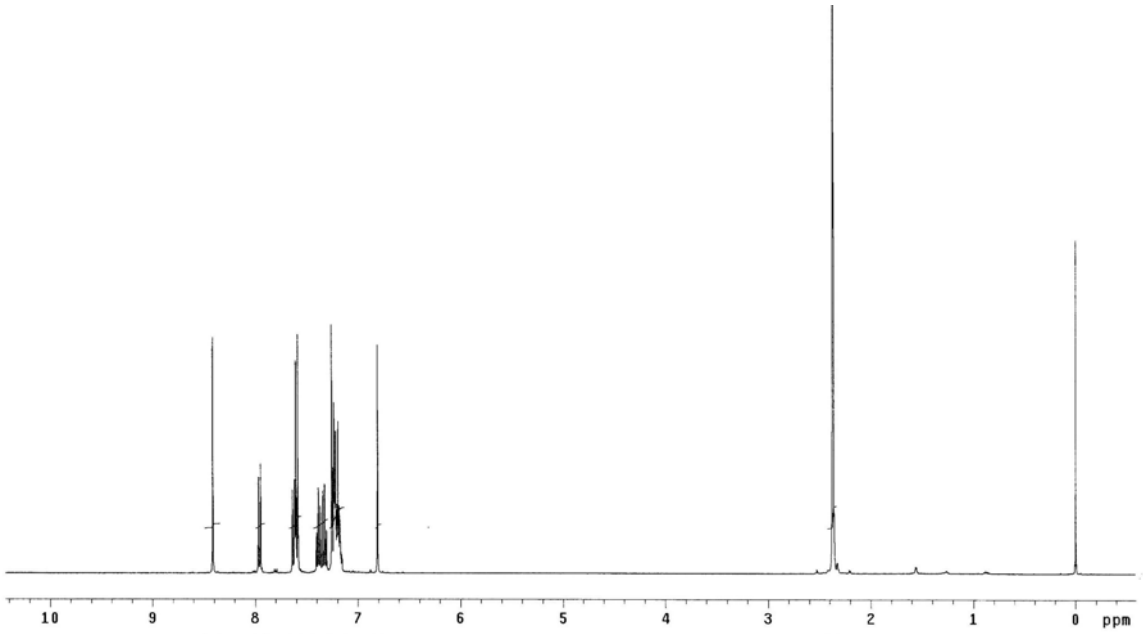


^{13}C NMR of **2.25b**

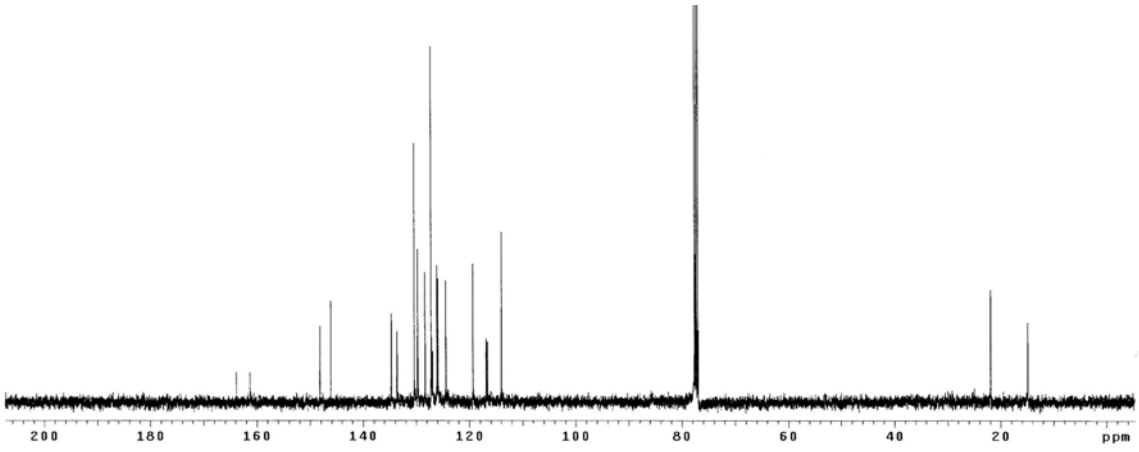


3[2-(4-Fluoro-3-methylphenyl)-2-nitrovinyl]-1-(toluene-4-sulfonyl)-1H-indole

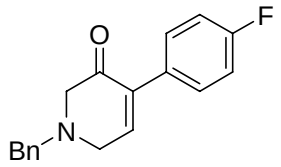
2.25c. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.39 (td, *J* = 1.2, 7.4 Hz, 1H), 7.32 (td, *J* = 1.2, 8.0 Hz, 1H), 7.21 (m, 4H), 3.37 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5 (d, *J* = 250.6, Hz), 148.1, 146.1, 134.7 (d, *J* = 8.9 Hz), 133.6, 133.5, 130.3, 129.7, 129.6, 128.3, 127.2, 126.9, 126.1, 125.9, 124.4, 119.3, 116.7 (d, *J* = 22.4 Hz), 113.9, 21.9, 14.9. FTIR (NaCl): 3142, 2925, 1644, 1599, 1500, 1447, 1378, 1318, 1242, 1175, 1139, 1093, 970, 906, 812, 747, 670 cm^{-1}. HRMS: calcd for $C_{24}H_{20}N_2O_4FS$ [M+1] 451.1128 found 451.1129. MP 182-183 °C yellow solid.



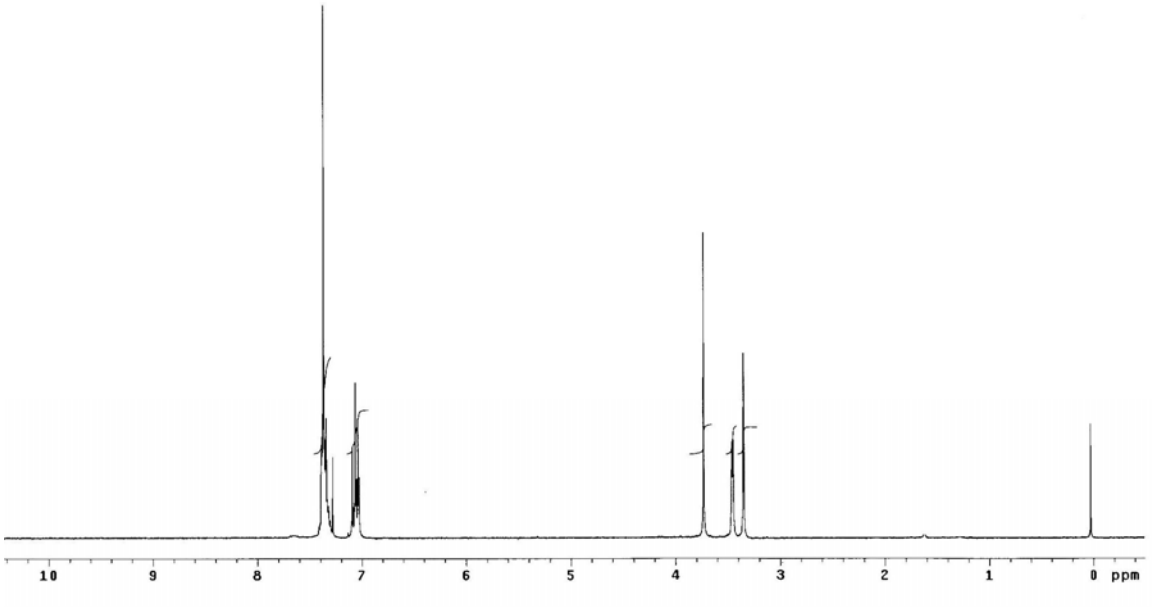
^{1}H NMR of **2.25c**



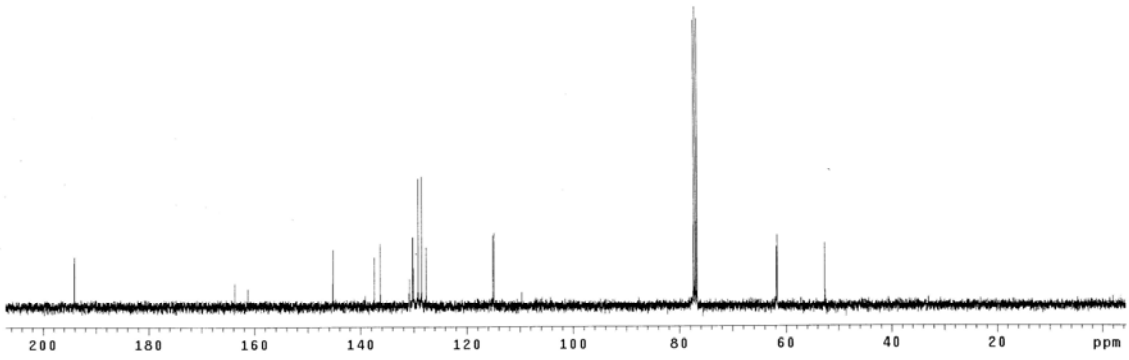
^{13}C NMR of **2.25c**



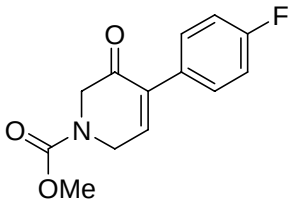
1-Benzyl-4-(4-fluorophenyl)-1,6-dihydro-*2H*-pyridin-3-one 2.33a.



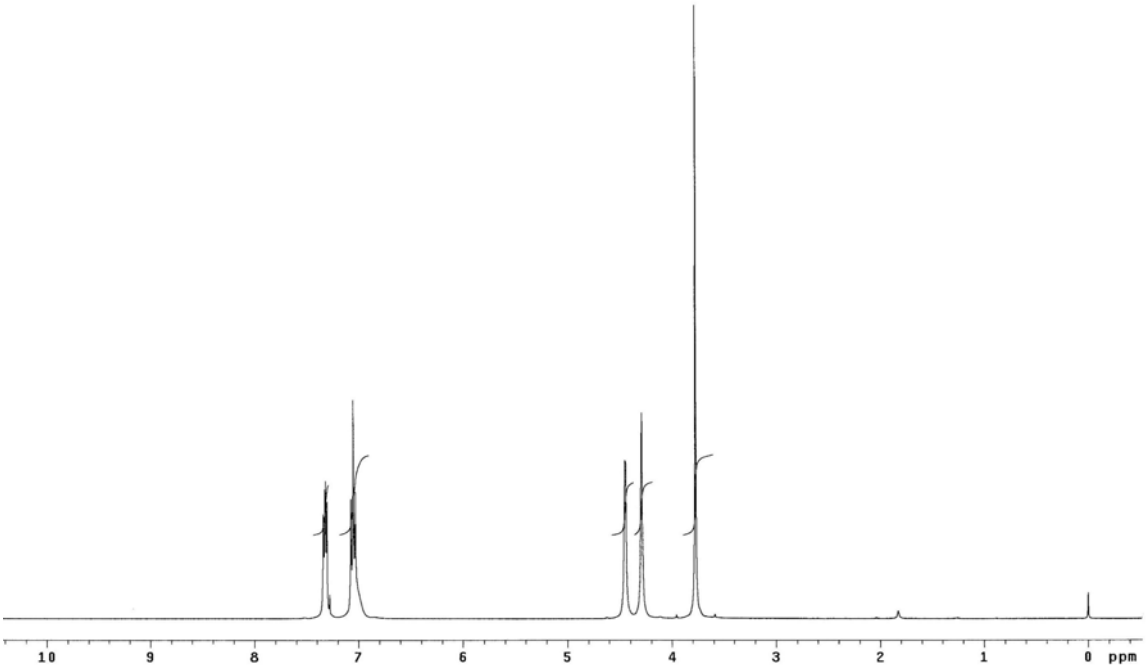
^{1}H NMR of **2.33a**



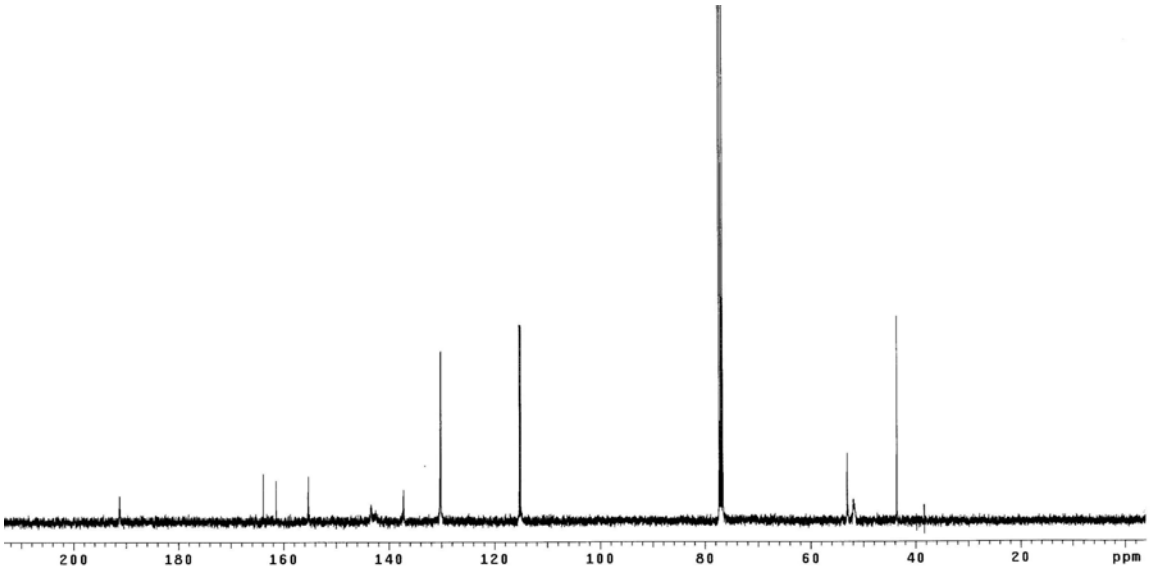
^{13}C NMR of **2.33a**



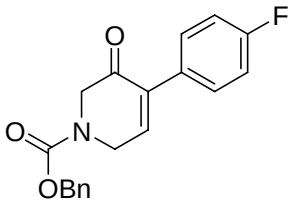
4-(4-Fluorophenyl)-3-oxo-3,6-dihydro-*2H*-pyridine-1-carboxylic acid methyl ester enone 2.33b.



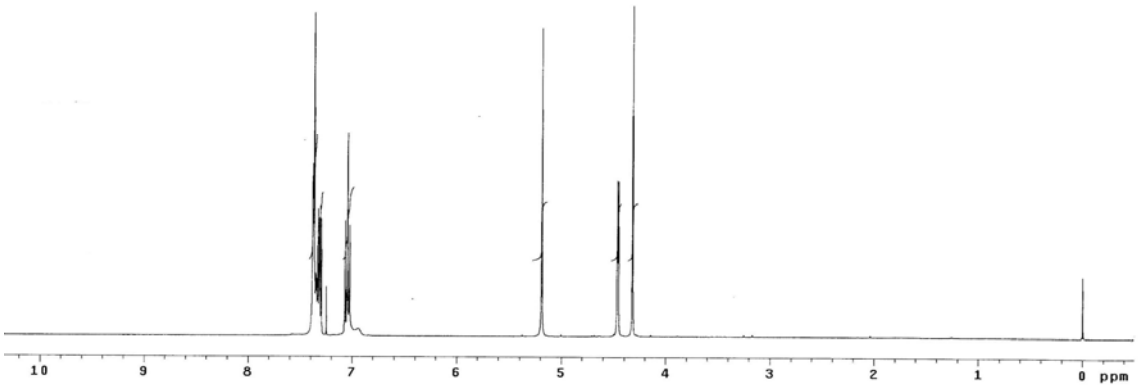
^{1}H NMR of **2.33b**



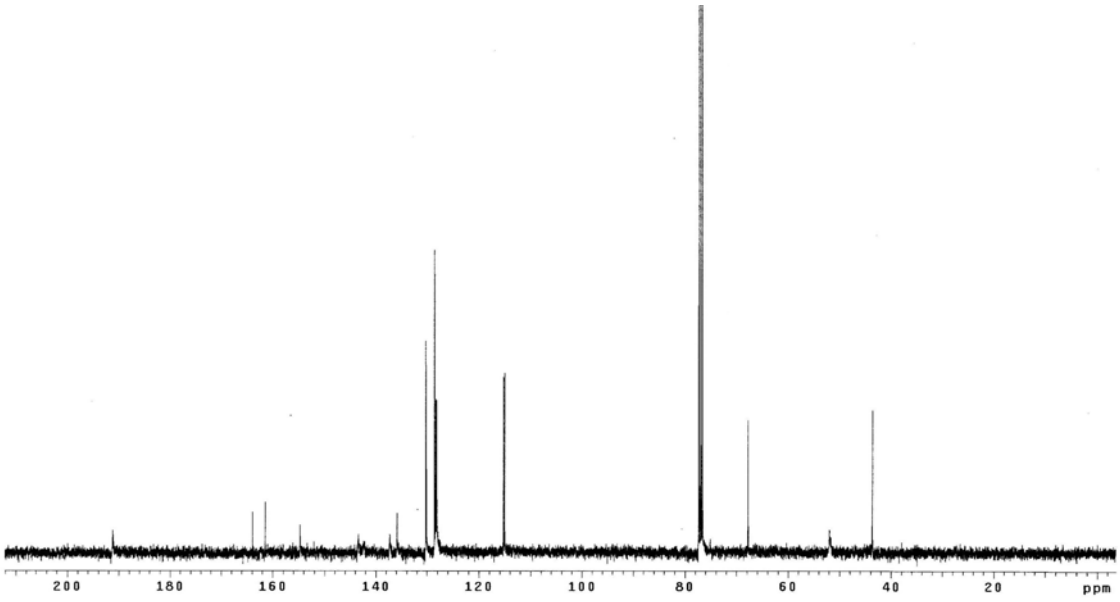
^{13}C NMR of **2.33b**



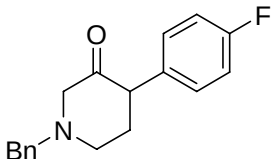
4-(4-Fluorophenyl)-3-oxo-3,6-dihydro-*2H*-pyridine-1-carboxylic acid benzyl ester 2.33c.



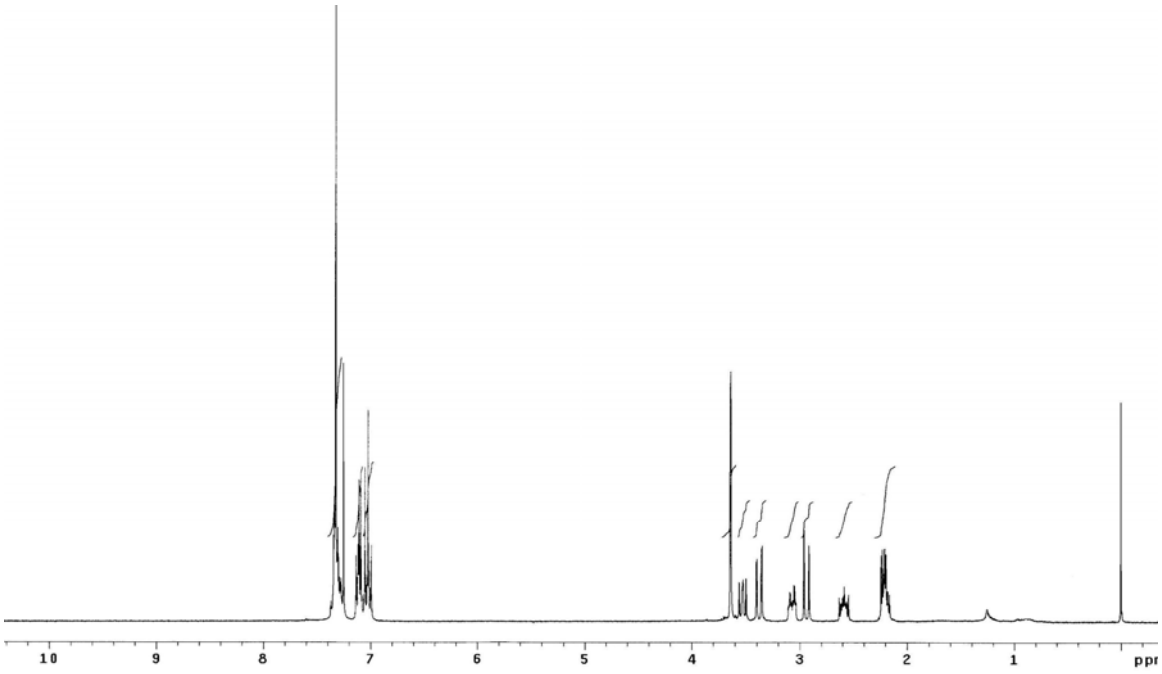
^{1}H NMR of **2.33c**



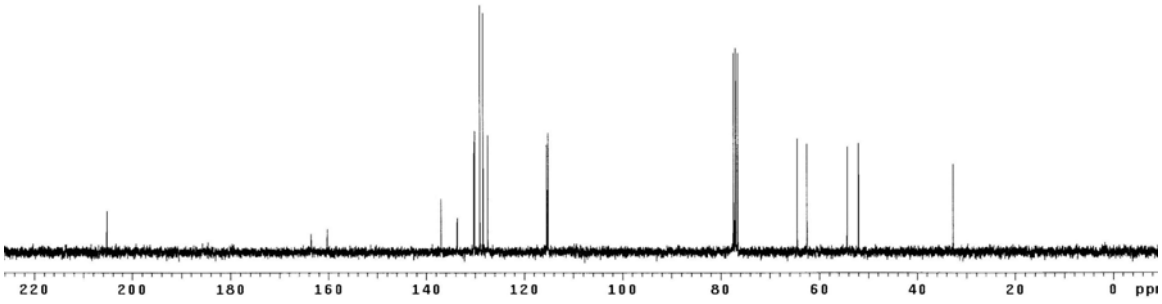
^{13}C NMR of **2.33c**



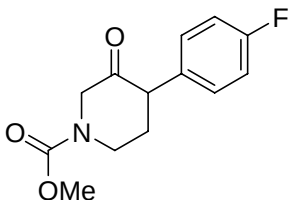
1-Benzyl-4-(4-fluorophenyl)piperidin-3-one 2.34a



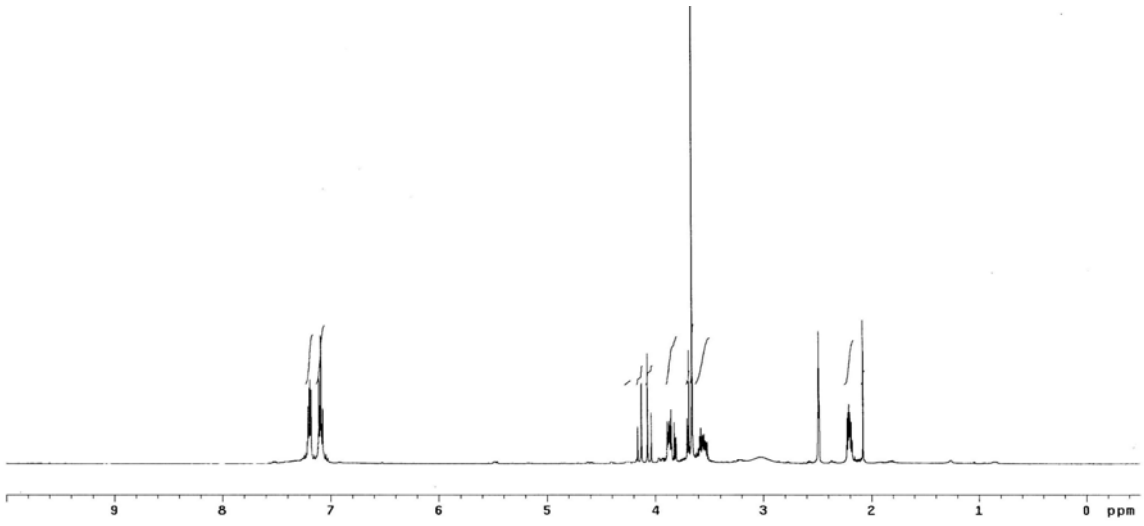
^{1}H NMR of **2.34a**



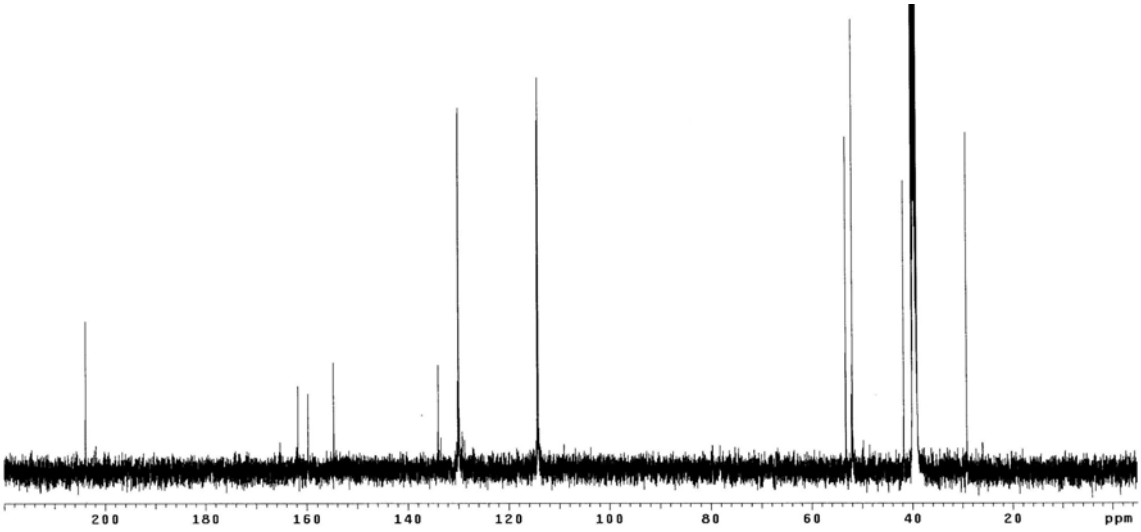
^{13}C NMR of **2.34a**



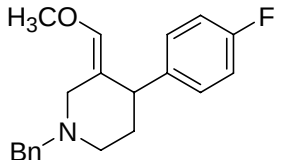
4-(4-Fluorophenyl)-3-oxo-piperidine-1-carboxylic acid methyl ester 2.34b



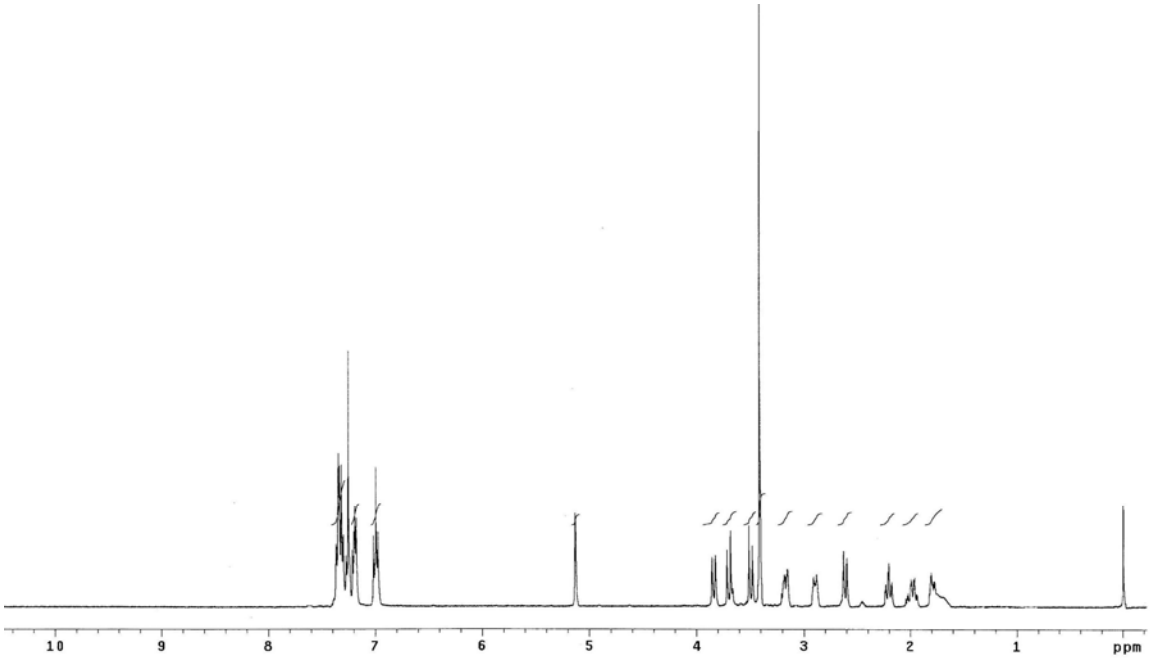
^{1}H NMR of **2.34b**



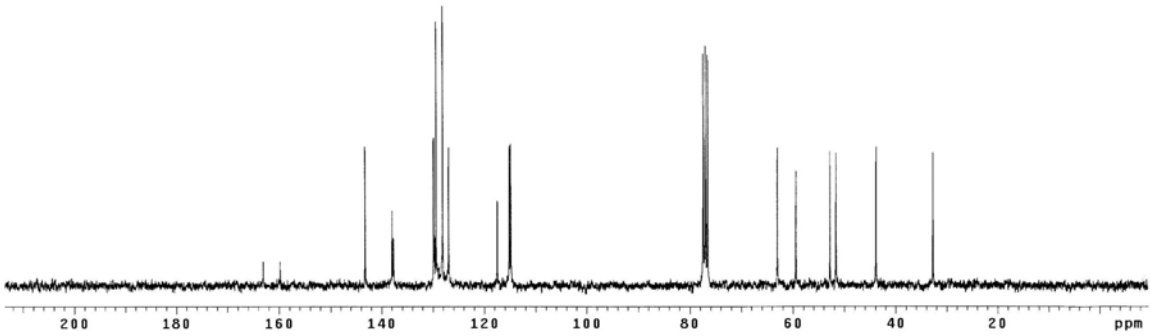
^{13}C NMR of **2.34b**



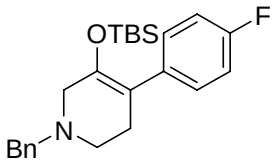
1-Benzyl-4-(4-fluorophenyl)-3-methoxymethylene piperidine 2.35



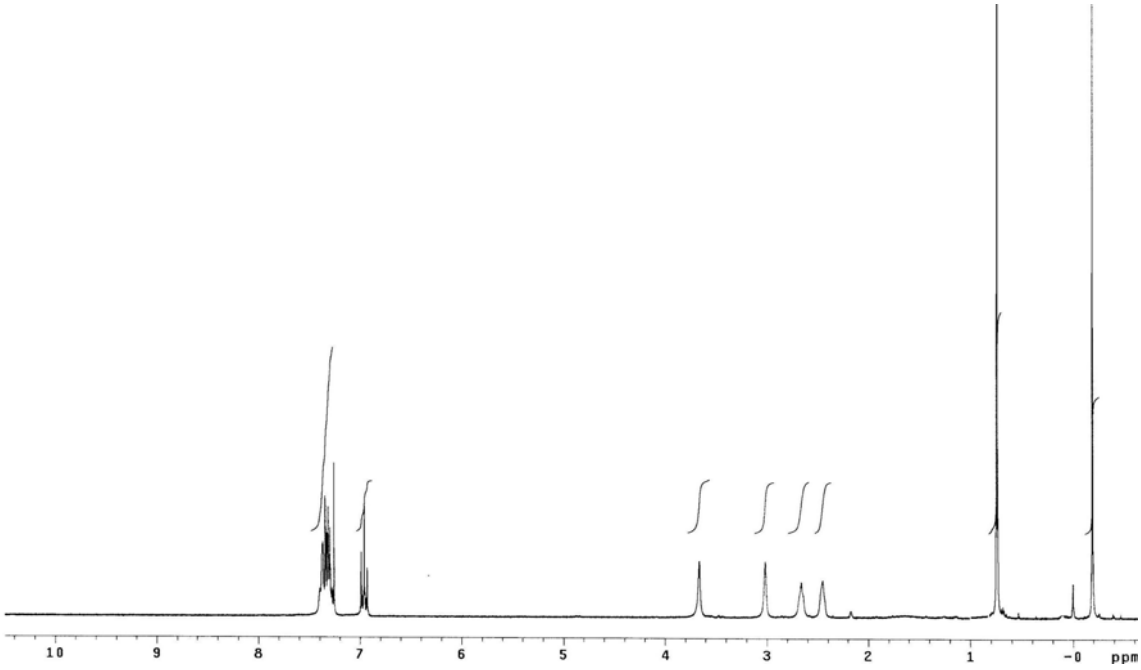
^{1}H NMR of **2.35**



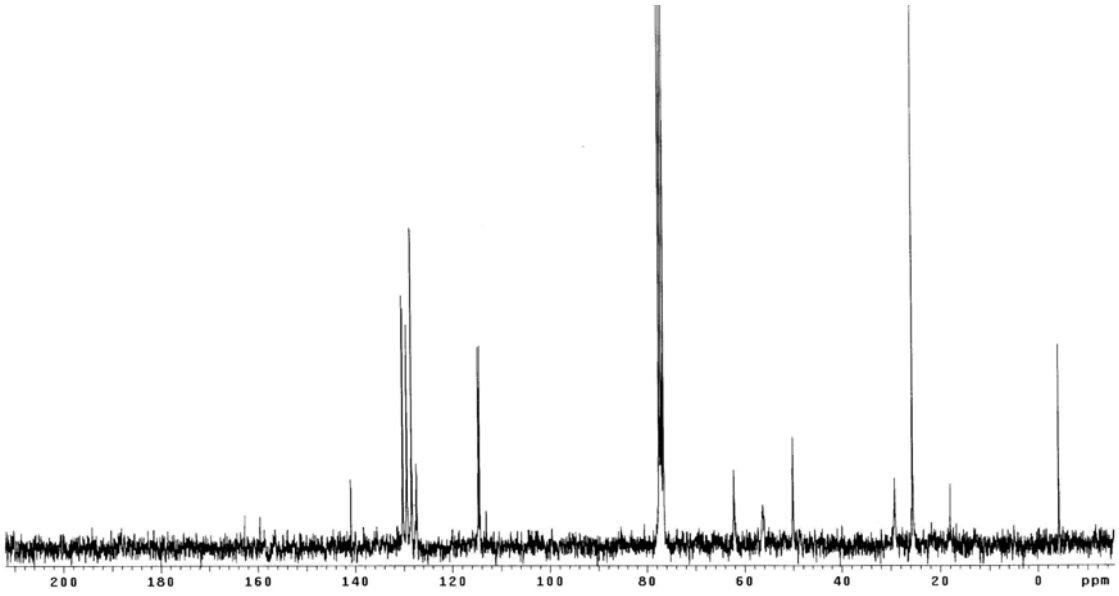
^{13}C NMR of **2.35**



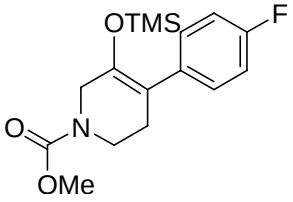
1-Benzyl-5-(*tert*-butyldimethylsilanyloxy)-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine 2.36a.



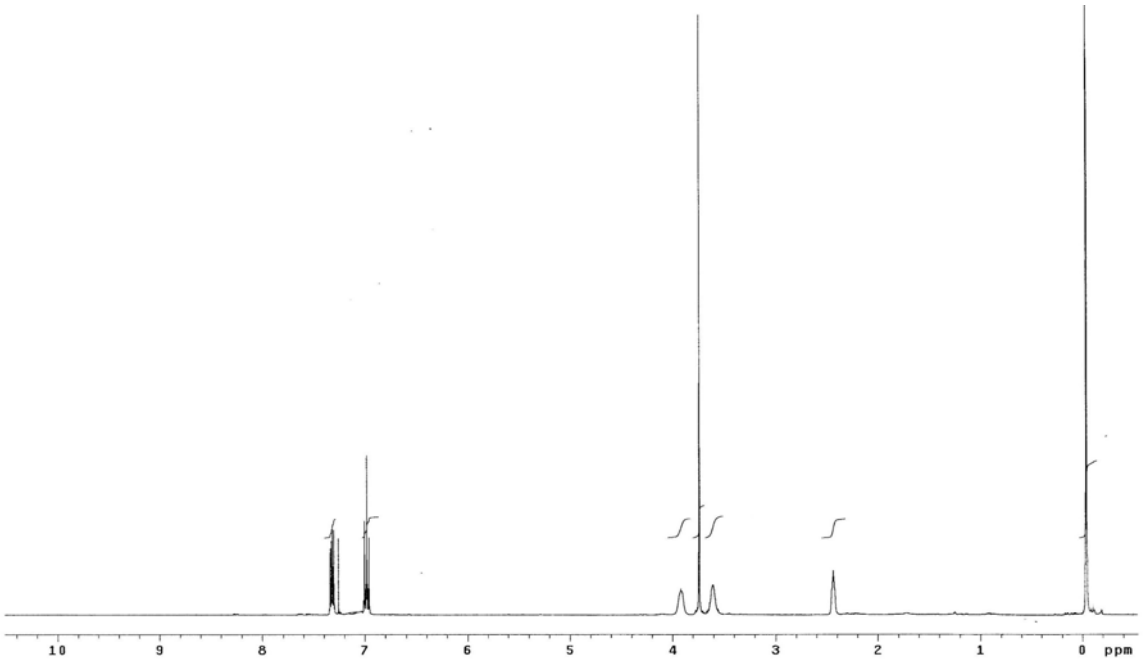
^{1}H NMR of **2.36a**



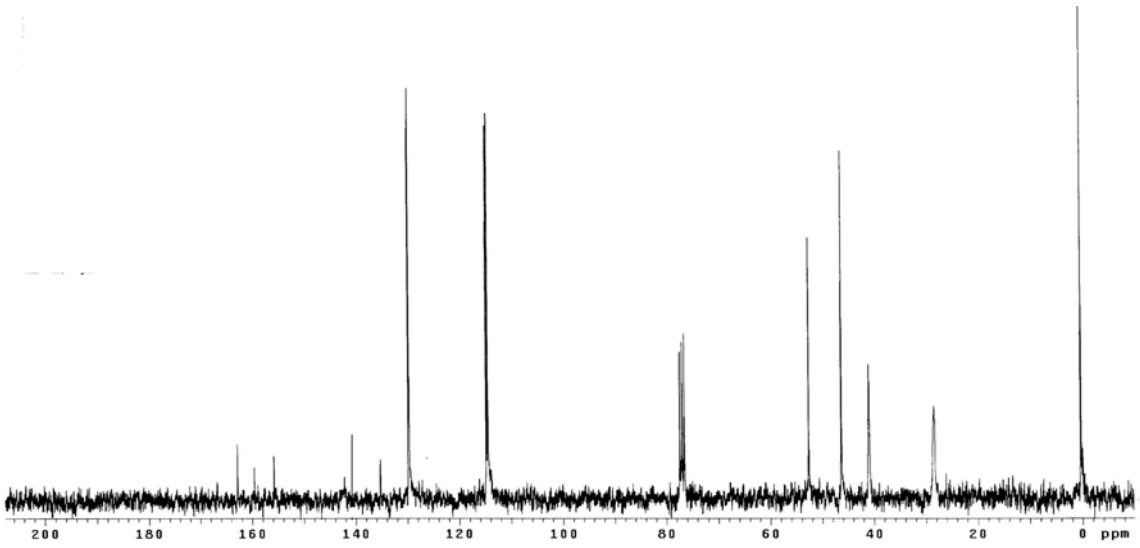
^{13}C NMR of **2.36a**



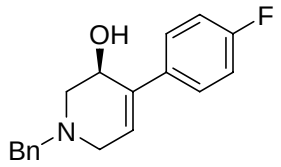
4-(4-Fluorophenyl)-5-trimethylsilanyloxy-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester 2.36b.



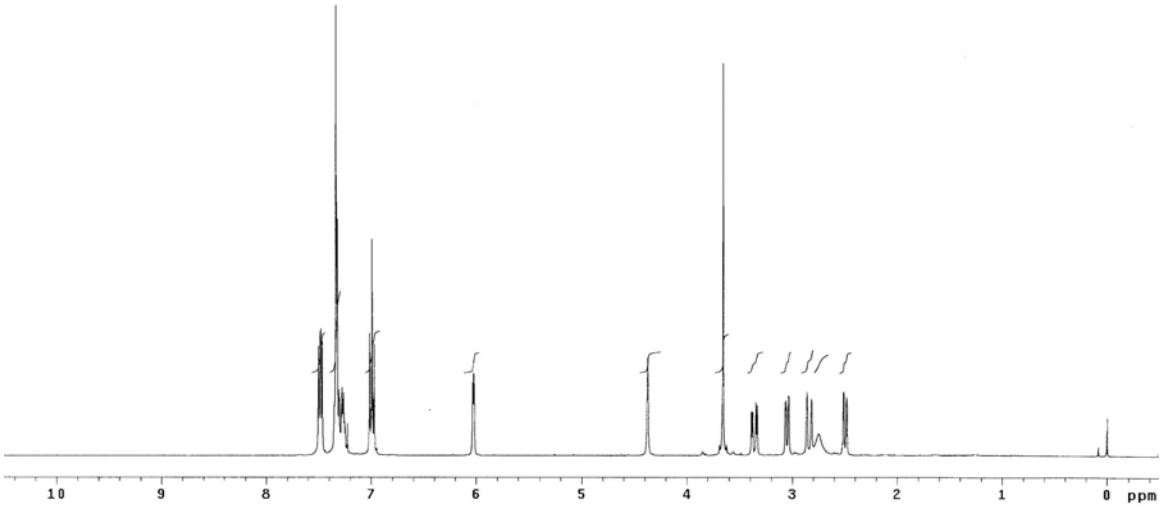
^{1}H NMR of **2.36b**



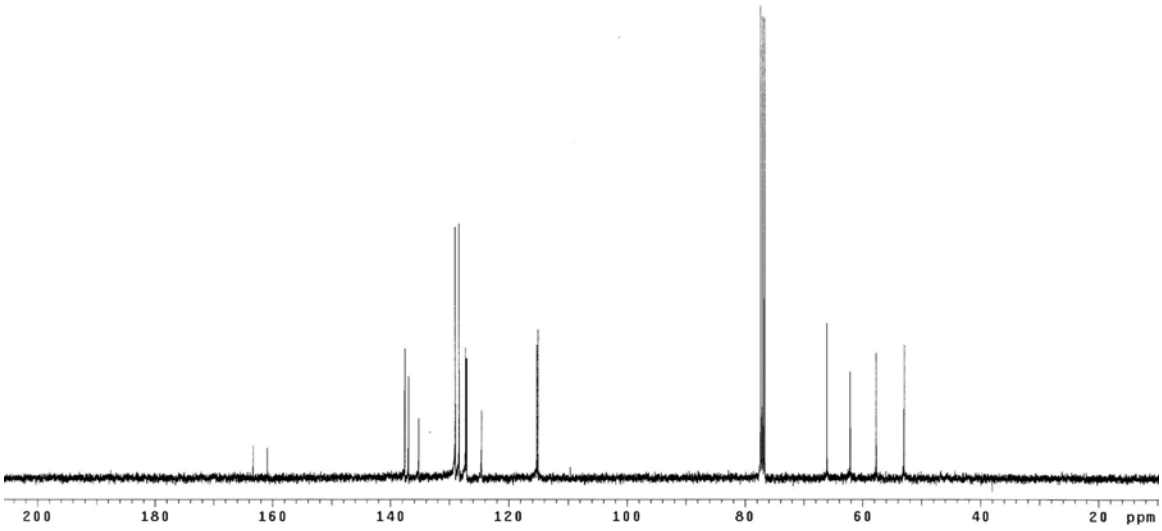
^{13}C NMR of **2.31b**



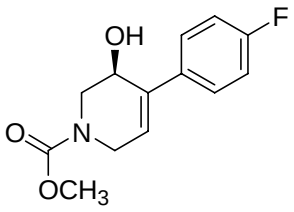
1-Benzyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridin-3-ol 2.37



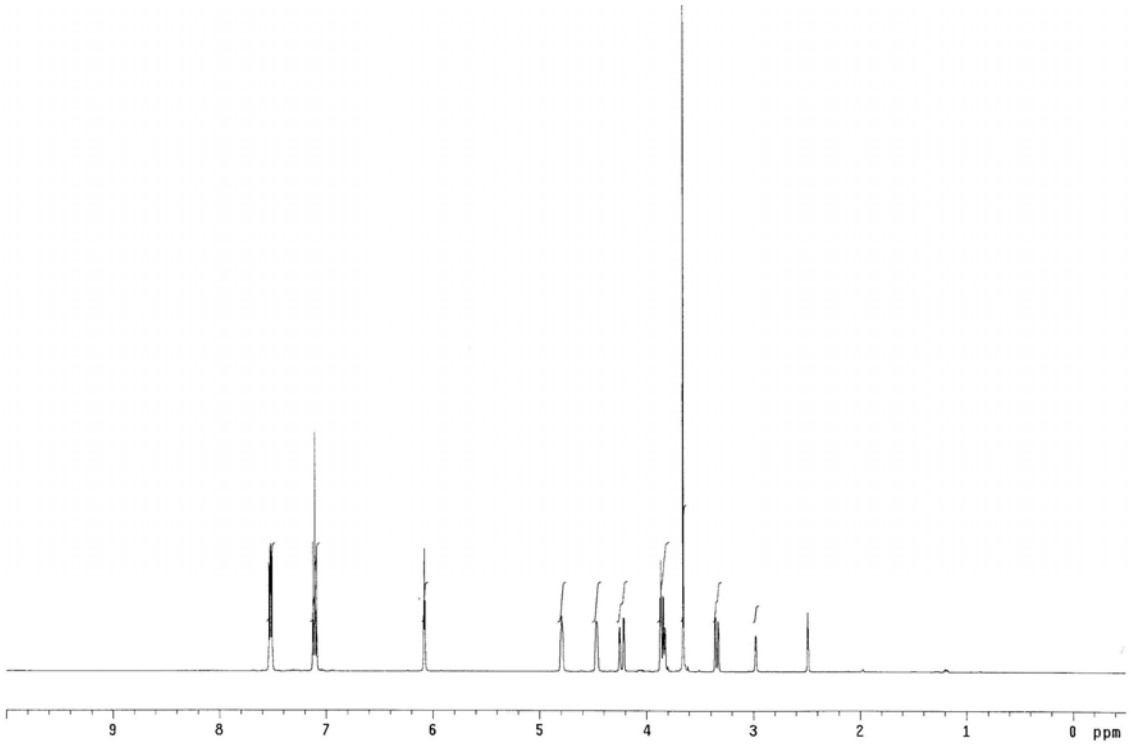
^{1}H NMR of **2.37**



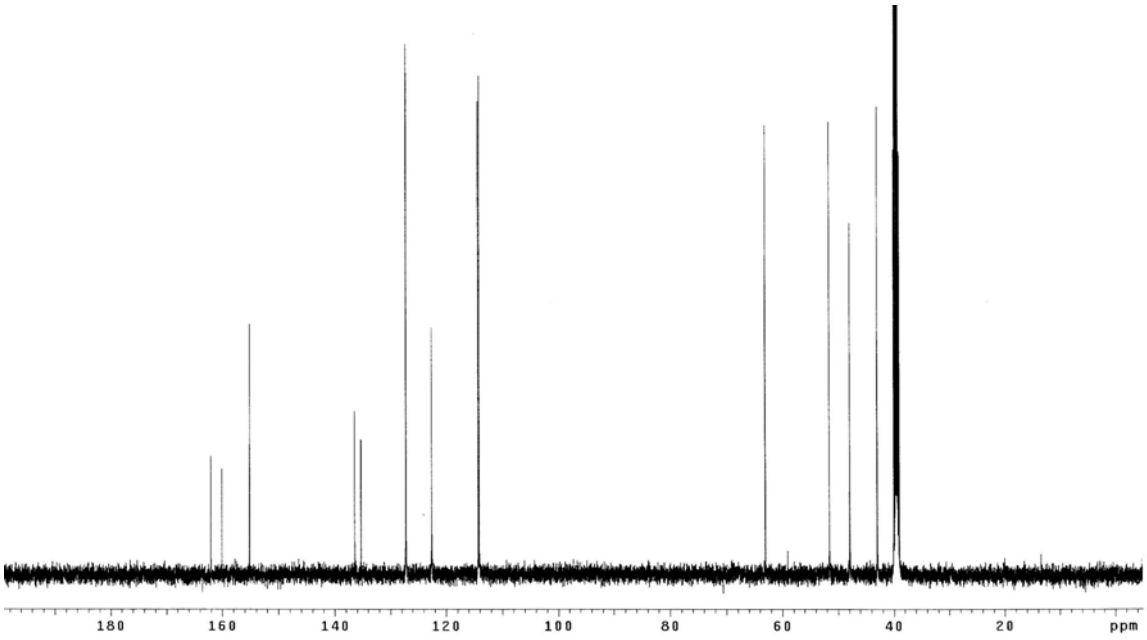
^{13}C NMR of **2.37**



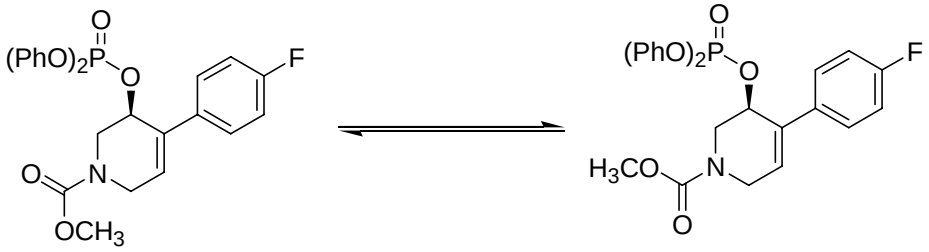
4-(4-Fluorophenyl)-3-hydroxy-3,6-dihydro-*2H*-pyridine-1-carboxylic acid methyl ester 2.38



^{1}H NMR of **2.38**

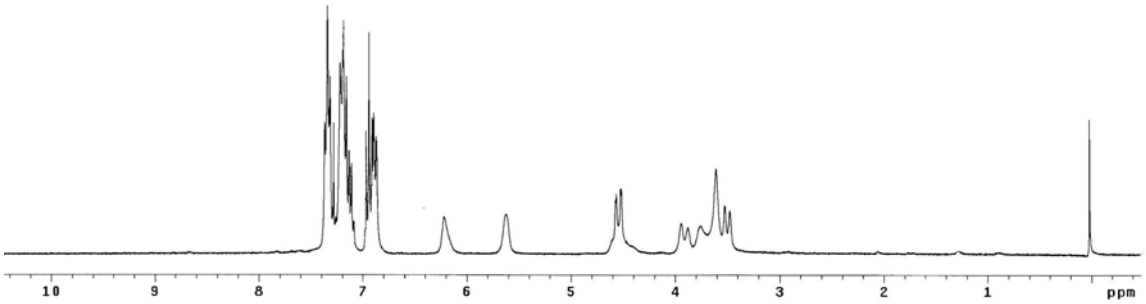


^{13}C NMR of **2.38**

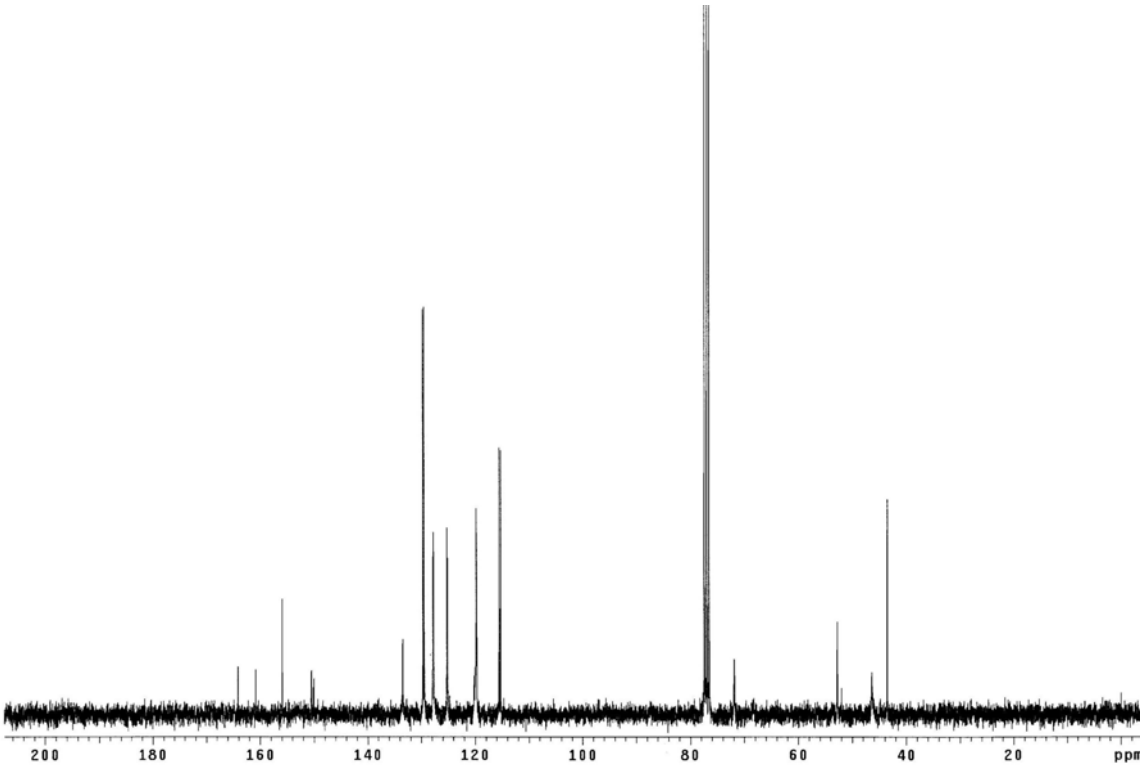


3-(Diphenoxyphosphoryloxy)-4-(4-fluorophenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester 2.39

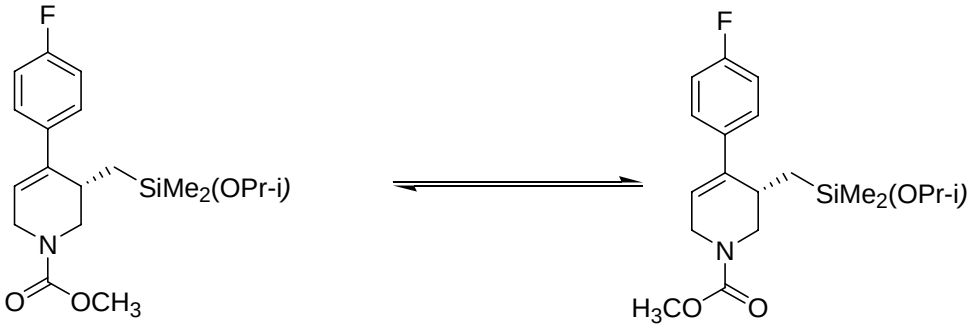
mixture of rotomers



^{1}H NMR of **2.39**

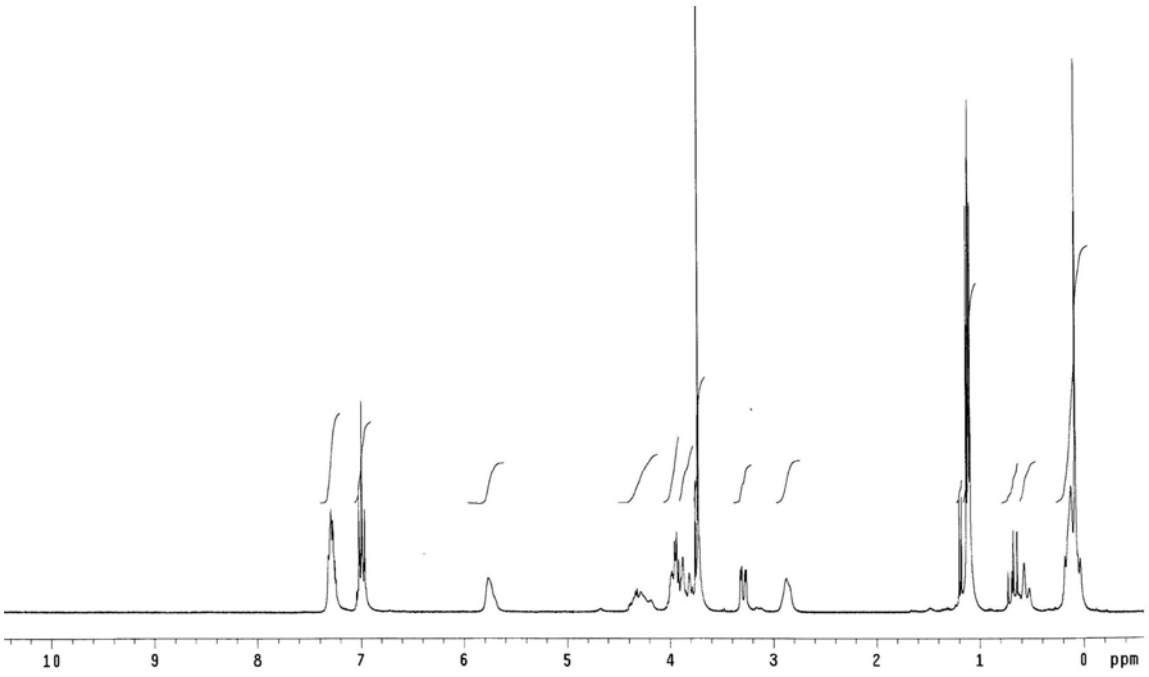


^{13}C NMR of **2.39**

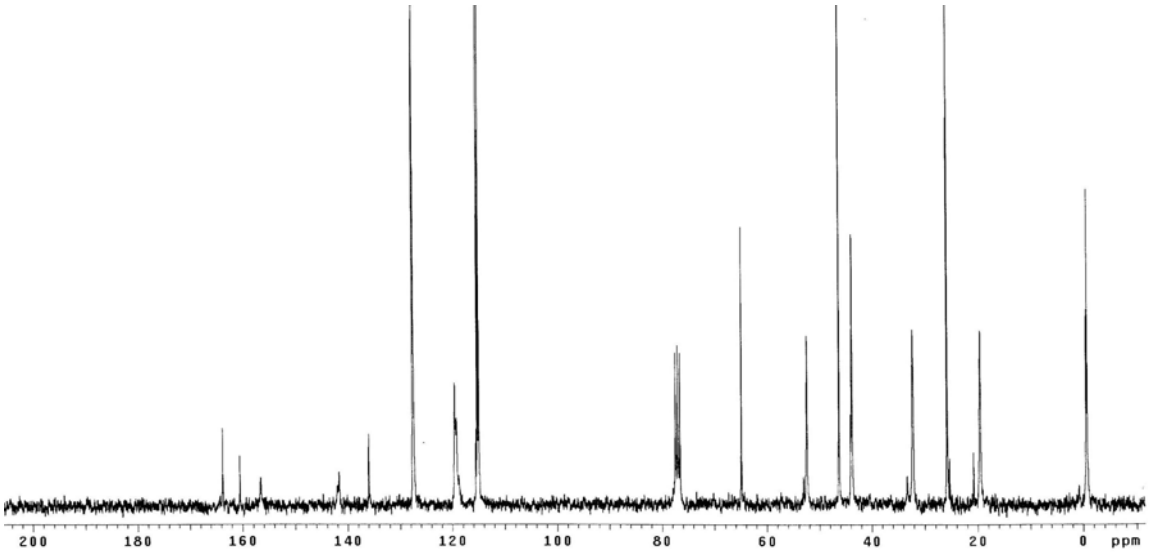


4-(4-Fluorophenyl)-3-[(isopropoxydimethylsilanyl)methyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester 2.40

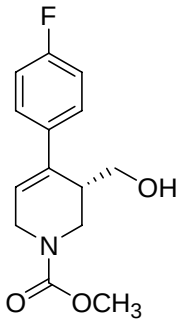
Mixture of rotomers



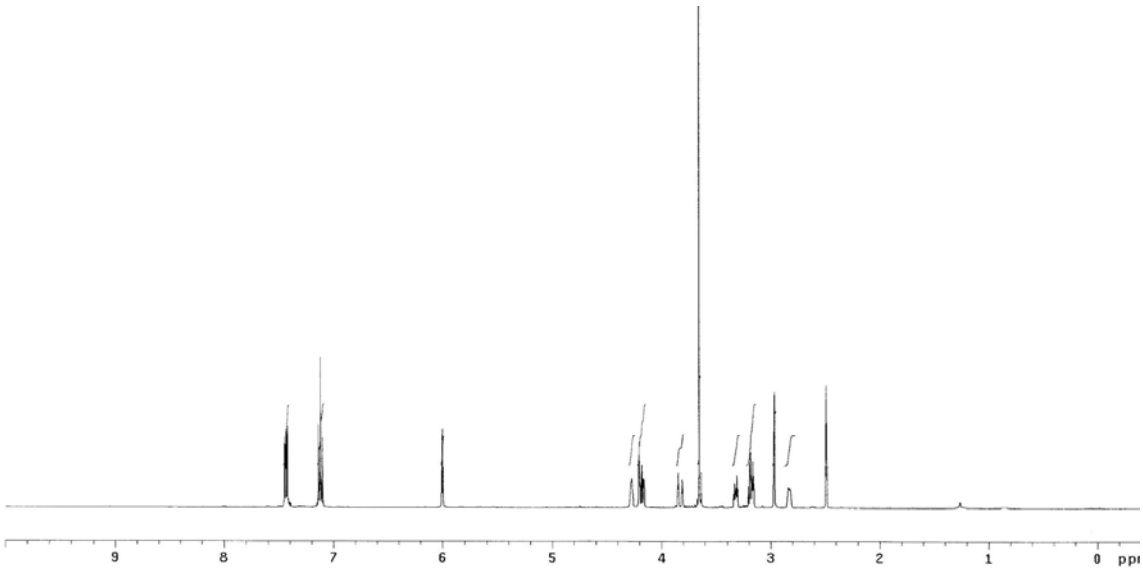
^{1}H NMR of **2.40**



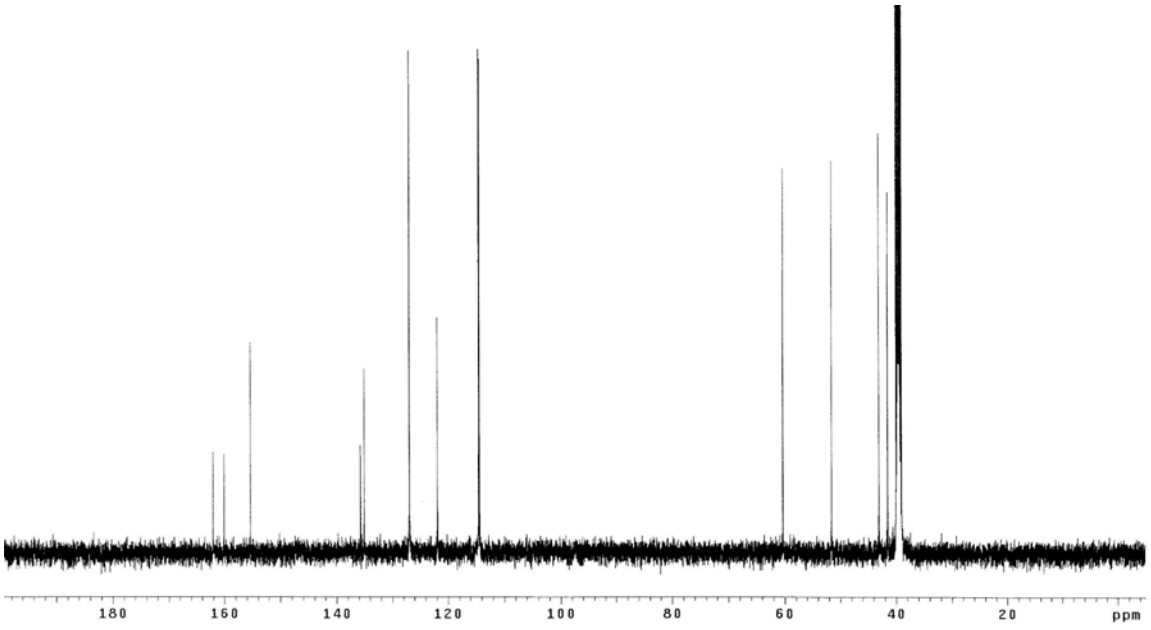
^{13}C NMR of **2.40**



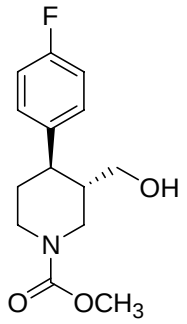
4-(4-Fluorophenyl)-3-hydroxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylic acid methyl ester 2.41



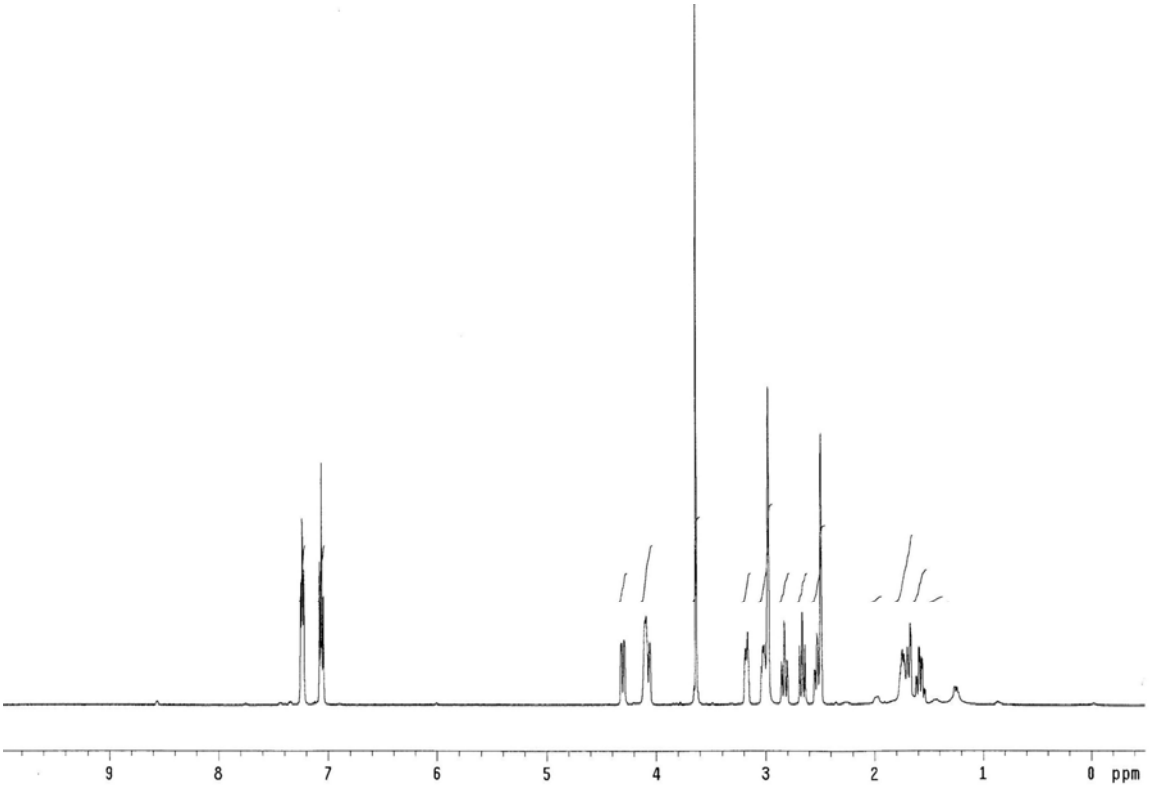
^{1}H NMR of **2.41**



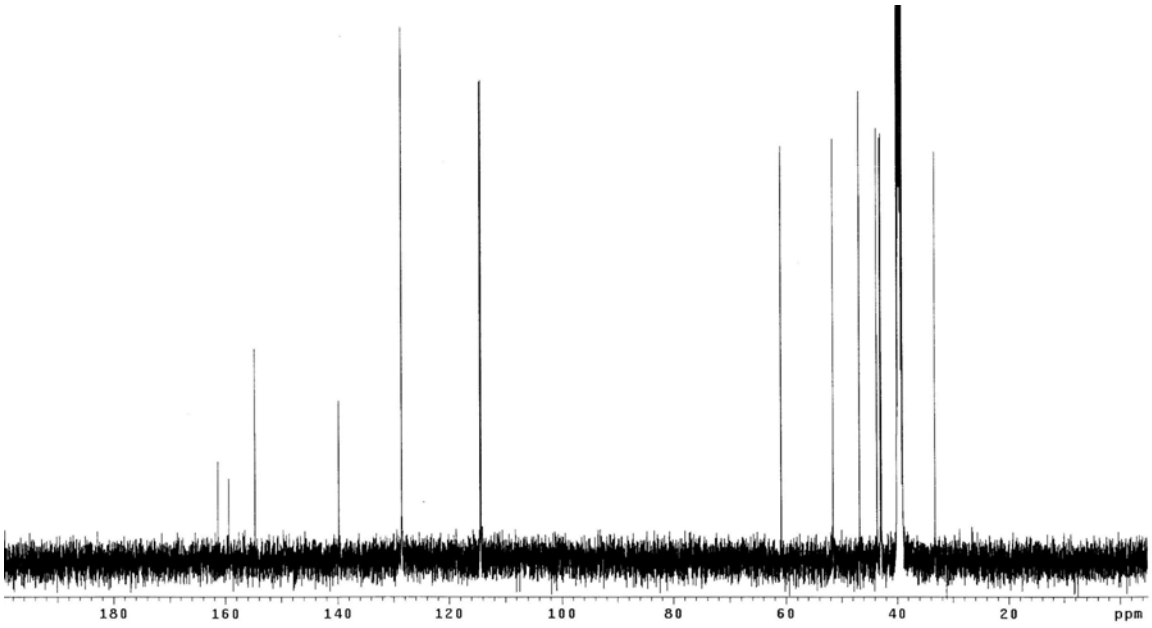
^{13}C NMR of **2.41**



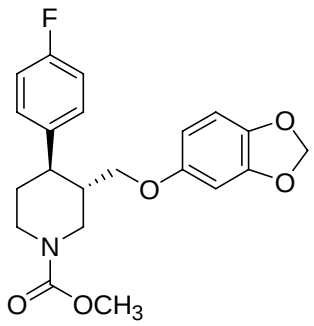
4-(4-Fluorophenyl)-3-hydroxymethylpiperidine-1-carboxylic acid methyl ester 2.42



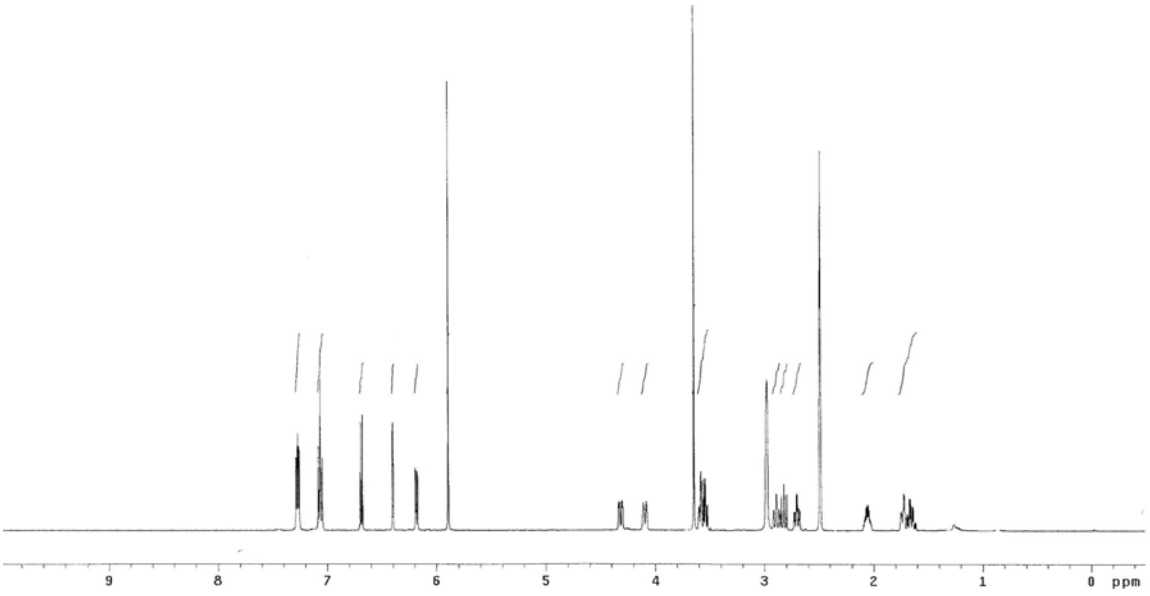
^{1}H NMR of **2.42**



^{13}C NMR of **2.42**



3-(Benzo[1,3]dioxol-5-yloxymethyl)-4-(4-fluorophenyl)piperidine-1-carboxylic acid methyl ester 2.43



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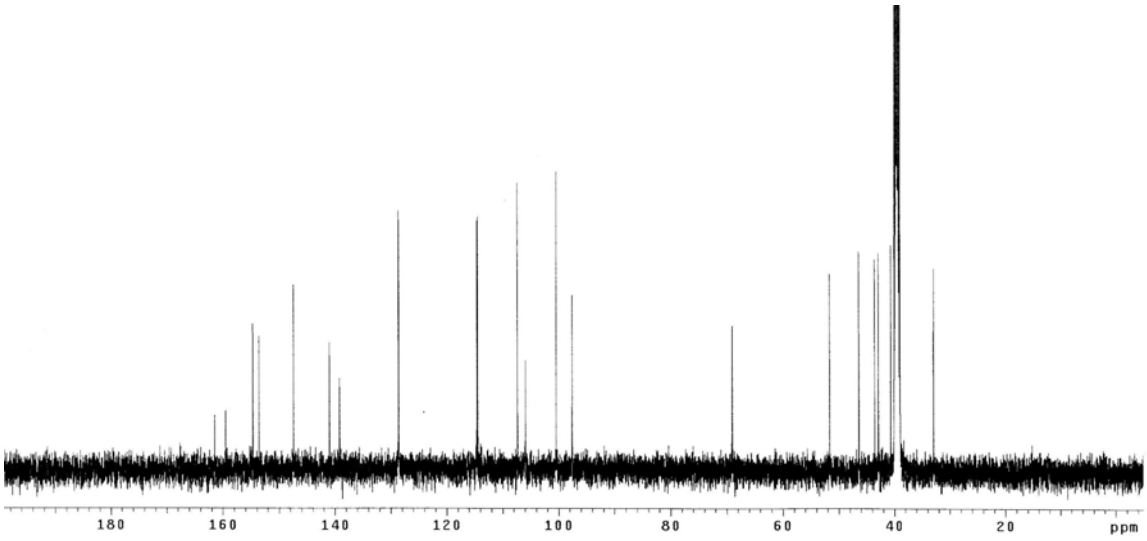
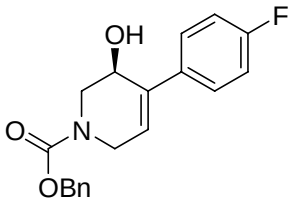
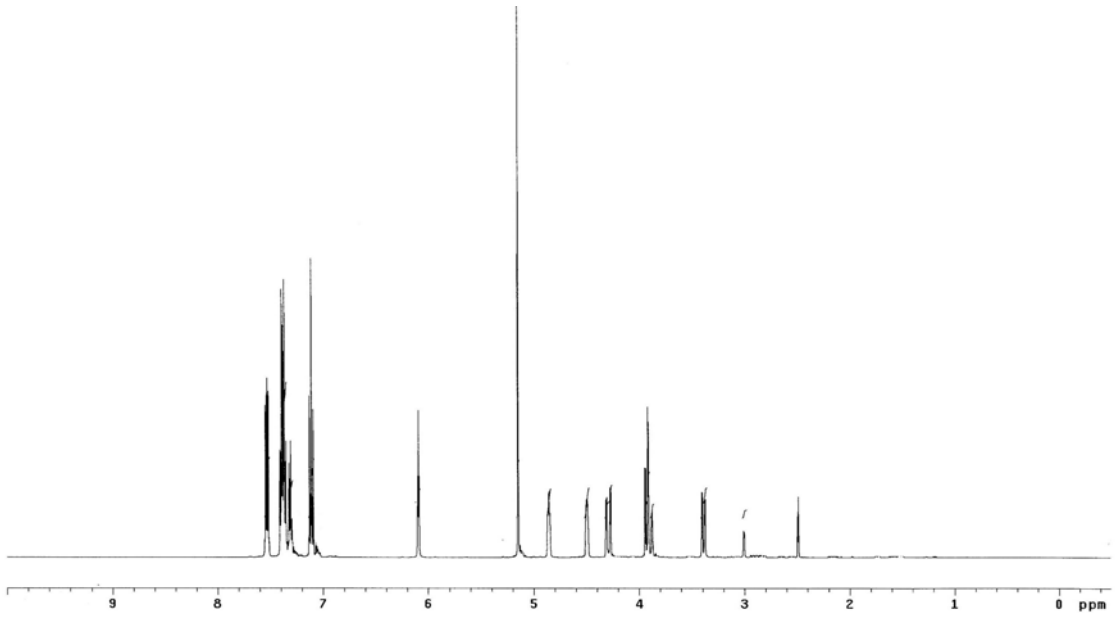


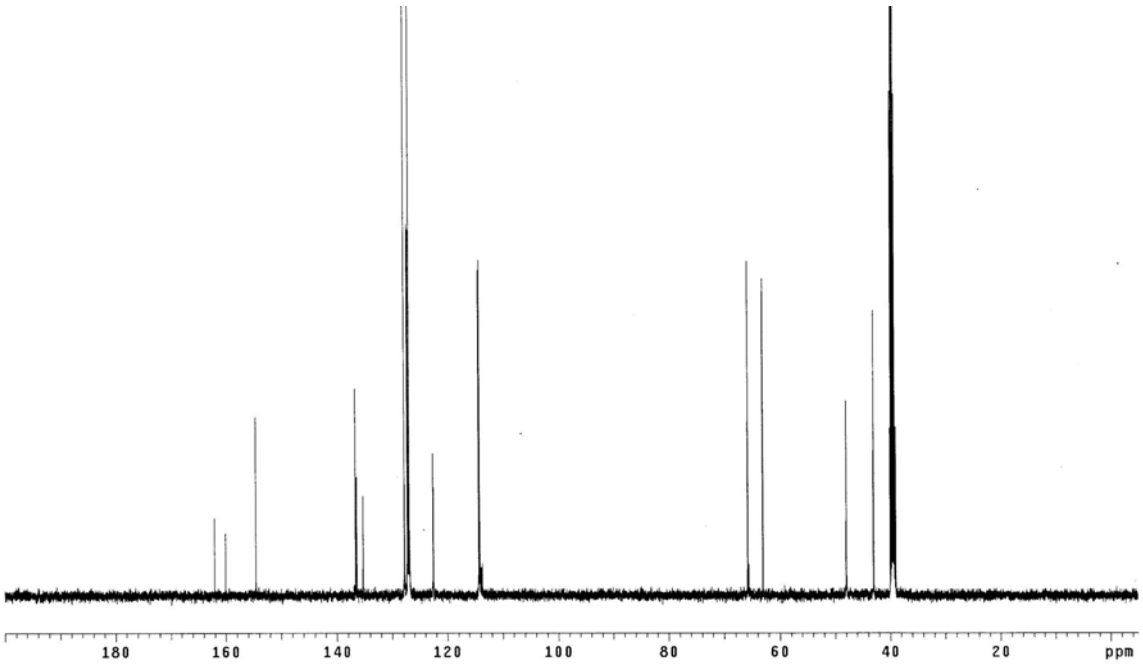
^{13}C NMR of **2.43**



4-(4-Fluorophenyl)-3-hydroxy-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester 2.44



^{1}H NMR of **2.44**



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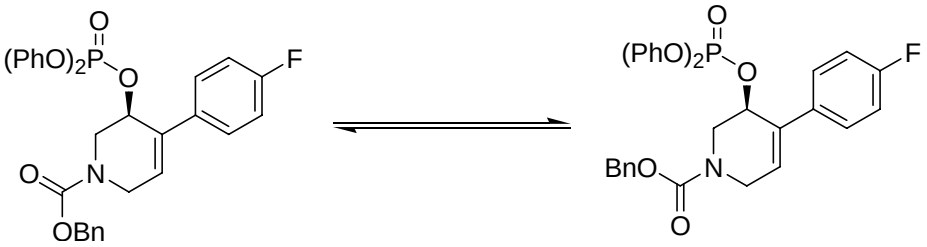
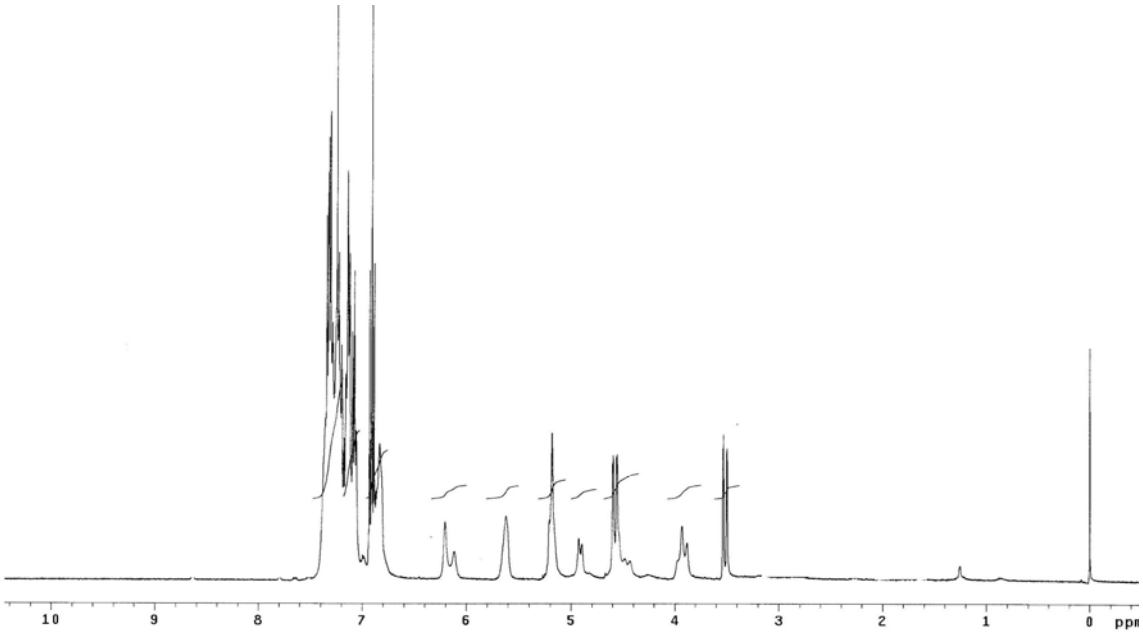
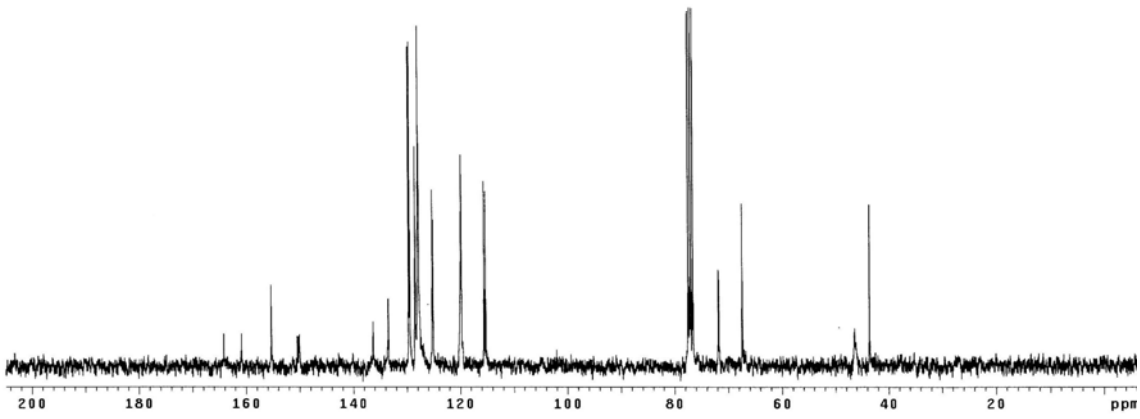


3-(Diphenoxyphosphoryloxy)-4-(4-fluorophenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester 2.45

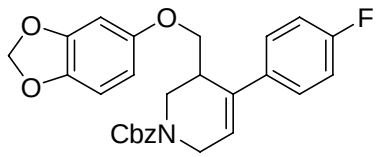
mixture of rotomers



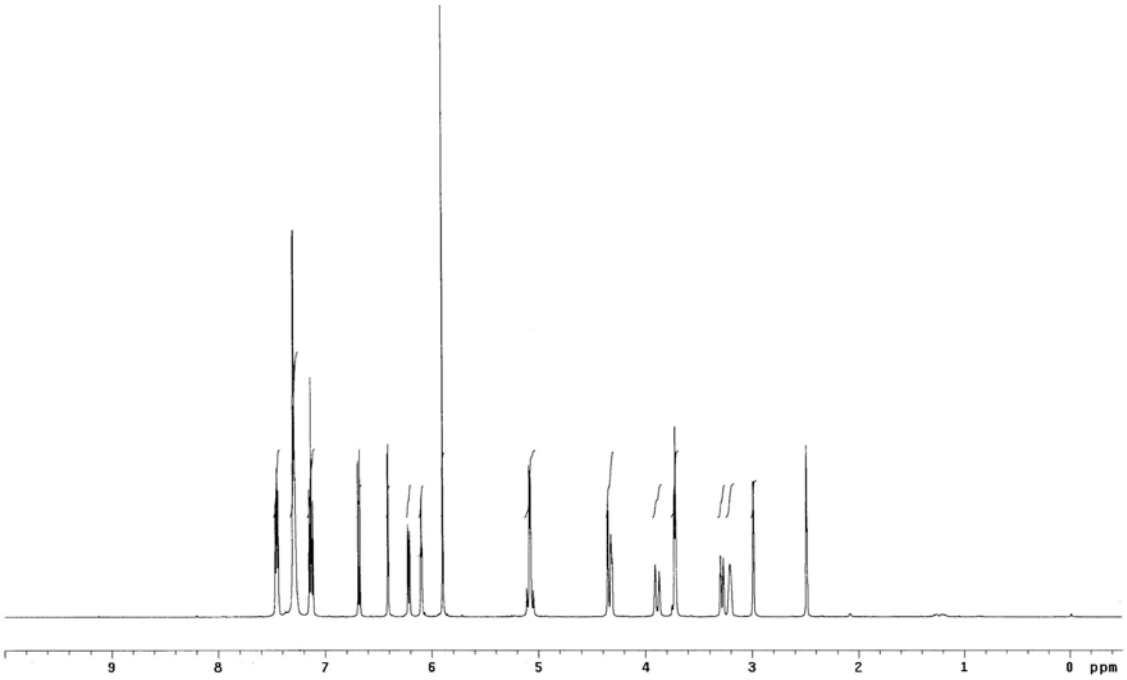
^{1}H NMR of **2.45**



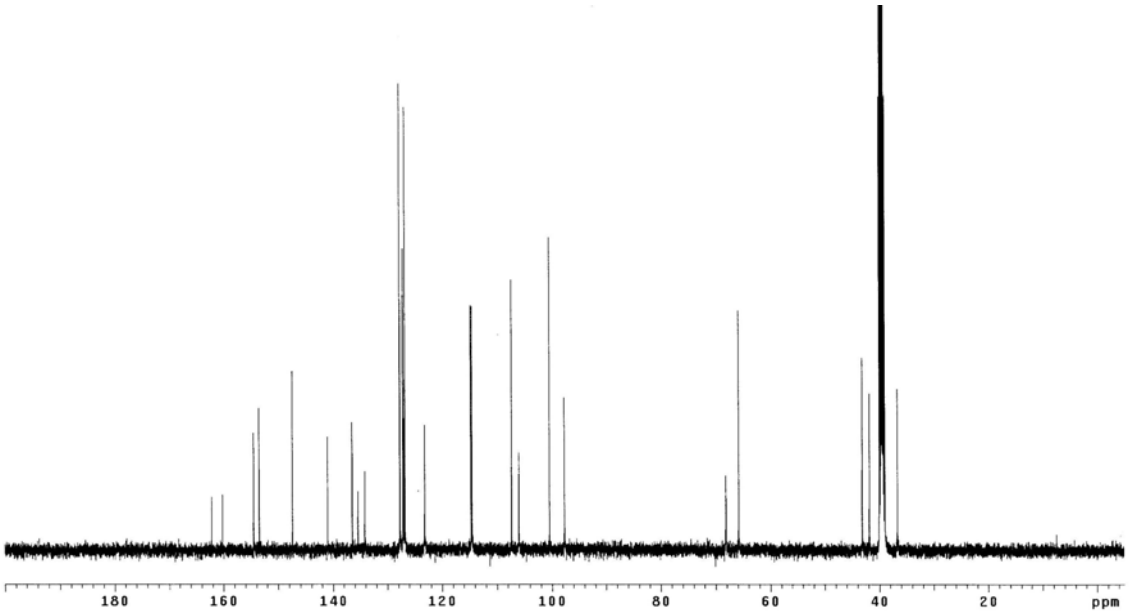
^{13}C NMR of **2.45**



3-(Benzo[1,3]dioxol-5-yloxymethyl)-4-(4-fluorophenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester 2.46



^{1}H NMR of **2.46**



^{13}C NMR of **2.46**

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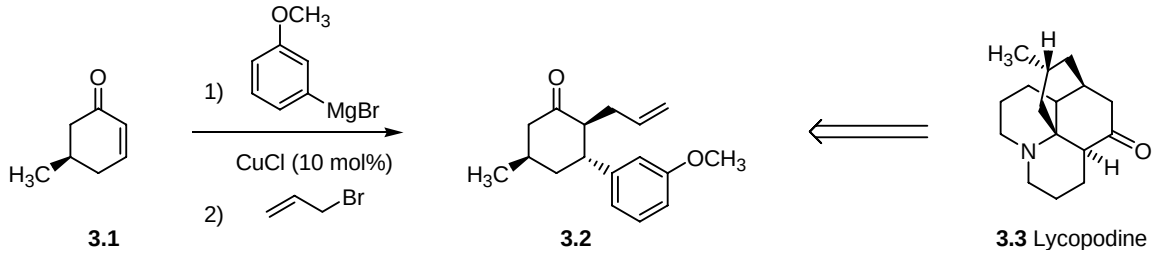
Chapter 3: Copper-Catalyzed Enantioselective Tandem Conjugate Addition-Arylation Using Bismuth(V) Reagents

3.1 Introduction

Tandem C-C bond forming transformations are attractive synthetic methods, as they enable a rapid increase in molecular complexity from readily available starting materials.[1,2] The advantage of these transformations is the ability to form several bonds and multiple contiguous stereogenic centers in a single manipulation utilizing a single catalyst without isolation and purification of the intermediates. The development of tandem transformations relies on latent functionality, meaning reaction on one site of a molecule induces a reaction at a different site. Potential functional groups for tandem reactions are enones, enals and enoates which can undergo conjugate addition (CA) followed by subsequent electrophilic trapping of the resulting nucleophilic enolate.[3] This type of tandem conjugate addition-electrophilic trapping strategy was first employed by Stork in the total synthesis of lycopodine (Scheme 3.1).[4]



3.1 **3.2** **3.3** Lycopodine

Scheme 3.1 Stork's application of tandem conjugate addition-alkylation in total synthesis of lycopodine

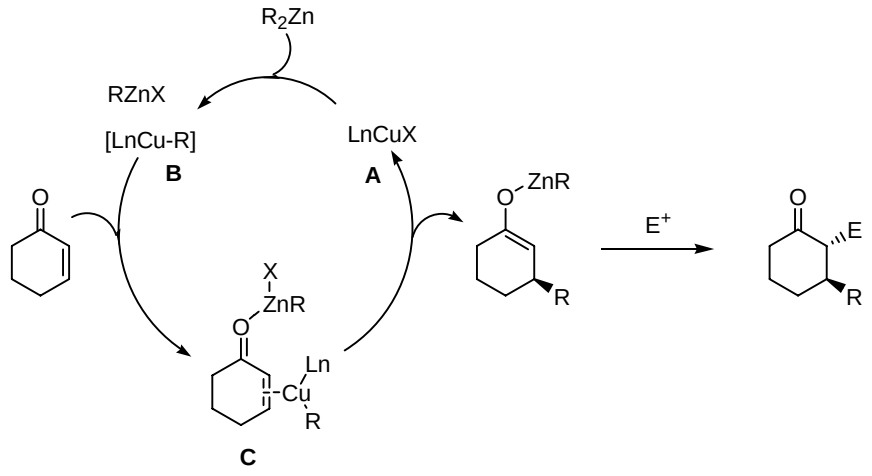
Subsequent to Stork's seminal report, application of conjugate addition-electrophilic trapping reaction has increased dramatically in the chemical literature.[5] Such methods include the copper-catalyzed conjugate addition of Grignard reagents to α,β-

unsaturated carbonyl compounds and trapping of the incipient enolates with classical electrophiles such as alkyl halides,[6] carbonyls,[7] acylating agents,[8] Michael acceptors,[9] and iminium ions.[10] These catalytic tandem conjugate addition-electrophilic trapping transformations are useful, however greater versatility and higher yields are obtained when stoichiometric organocuprate reagents are employed. Additionally, these reactions are not enantioselective. In the last decade catalytic asymmetric conjugate addition methods have received considerable interest and the Krische group has made contributions to this field.

3.2 Asymmetric Copper-Catalyzed Tandem Conjugate Addition-Electrophilic Trapping Reactions

3.2.1 Mechanistic Features

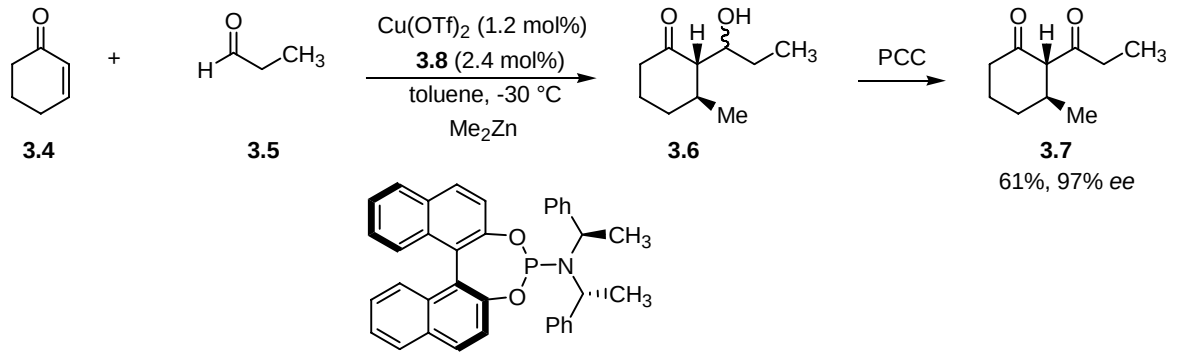
Catalytic conjugate addition of Grignard reagents to α,β-usaturated carbonyl compounds is one of the oldest and well developed transformations. However, asymmetric variants of these transformations are under developed. Conversely, in the last decade, highly enantioselective Cu-catalyzed conjugate addition reaction of organozinc reagents to α,β-unsaturated carbonyl compounds have been studied extensively.[11] Effective methods for asymmetric conjugate addition of alkylzinc reagents to cyclic enones,[12] including the more challenging cyclopentenones,[13] lactones,[14] nitroalkenes,[15] and acyclic enones[16] have been developed. A simplified mechanism for asymmetric conjugate addition starts with a chiral copper(I) complex **A**, alkyl transfer from R_2Zn to this copper complex **A** results in alkylcopper complex **B** (Scheme 3.2). Simultaneous complexation of the enone carbonyl by the alkylzinc fragment and the coordination of the alkylcopper complex to the π-bond give the bimetallic complex **C**. This bimetallic complex provides a rigid transition state which translates to high levels of stereocontrol. Subsequent alkyl transfer to the β-terminus of the enone generates a zinc enolate, which can be trapped by a variety of electrophiles such as aldehydes, ketones, carboxylates and alkyl halides in tandem protocols.



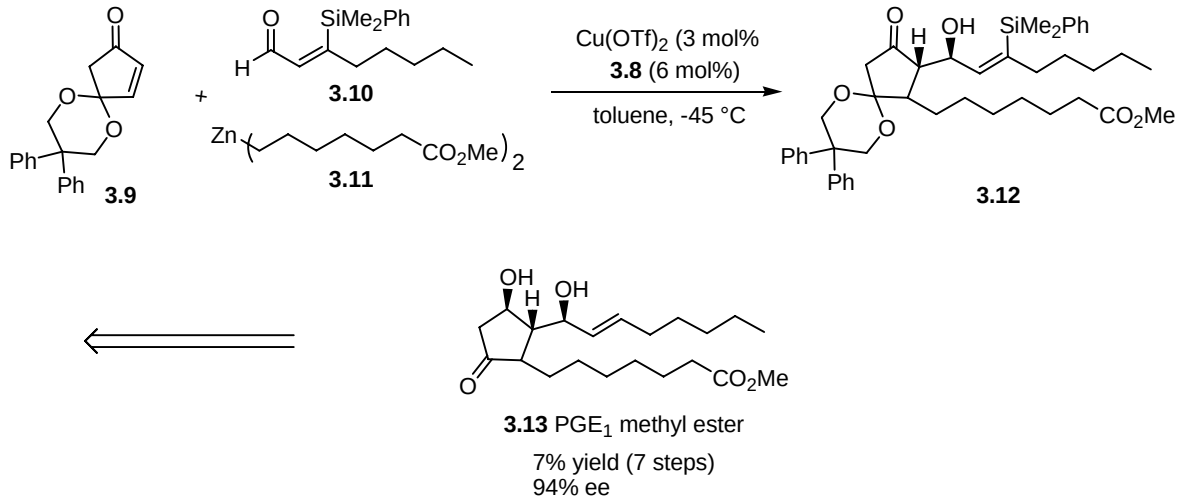
Scheme 3.2 Catalytic cycle for copper-catalyzed conjugate addition of organozinc reagents to enones

3.2.2 Copper-Catalyzed Asymmetric Tandem Conjugate Addition-Electophilic Trapping Reactions Involving Organozinc Reagents

In 1997 Feringa and co-workers reported the first catalytic asymmetric tandem conjugate addition of organozinc reagents to α,β–usaturated carbonyl compounds with subsequent trapping of the resulting enolate with aldehydes (Scheme 3.3).[17] This asymmetric tandem conjugate addition-aldol reaction involving dimethylzinc and 2-cyclohexenone **3.4** provides *trans*-2,3-disubstituted cyclohexanone **3.6** in the presence of a copper(I) salt and phosphoramidite ligand **3.8**. In this transformation complete control of both relative and absolute stereochemistry is achieved in vicinal functionalization of both cyclohexenone and cyclopentenone. The synthetic utility of the asymmetric tandem conjugate addition/aldol was demonstrated in total synthesis of PGE_1 (prostaglandin E1) methyl ester (Scheme 3.4).[13a, 17d]



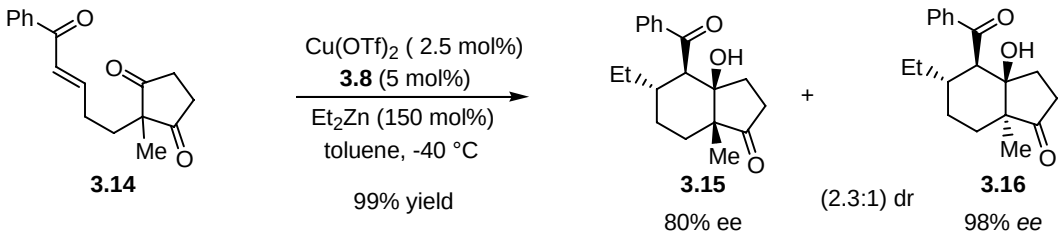
Scheme 3.3 The asymmetric tandem conjugate addition-aldol involving organozinc reagents



Scheme 3.4 Application of asymmetric tandem conjugate addition-aldol reaction in total synthesis of PGE_1 methyl ester

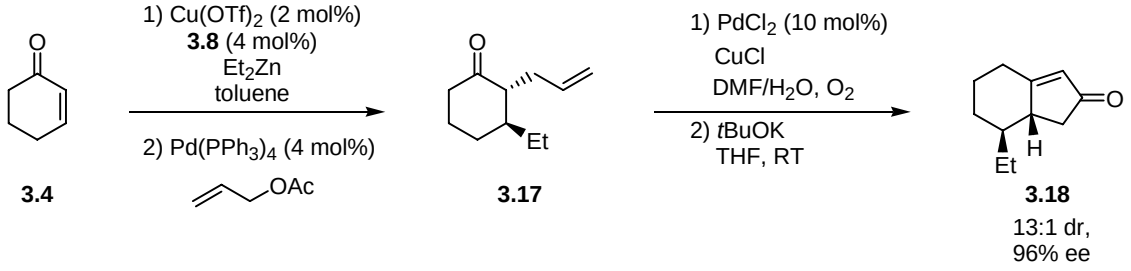
In 2004 Krische and co-workers reported a copper-catalyzed conjugate addition/intramolecular electrophilic trapping transformation that utilize ketones, esters and nitriles as terminal electrophiles (Scheme 3.5).[18] Enone substrates containing an appendant ketone, ester or nitrile functionality undergo conjugate addition in the presence of organozinc reagents and catalytic $Cu(OTf)_2/P(OEt)_3$ followed by electrophilic trapping

to provide bicyclic products in excellent yields and modest diastereoselectivity. When the phosphoramidite lingand **3.8** is used in place of $P(OEt)_3$, asymmetric tandem conjugate addition-aldol is achieved in high yields and excellent enantioselectivity. This transformation represents the first use of ketones, esters and nitriles as electrophiles in copper-catalyzed conjugate addition-electrophilic trapping.



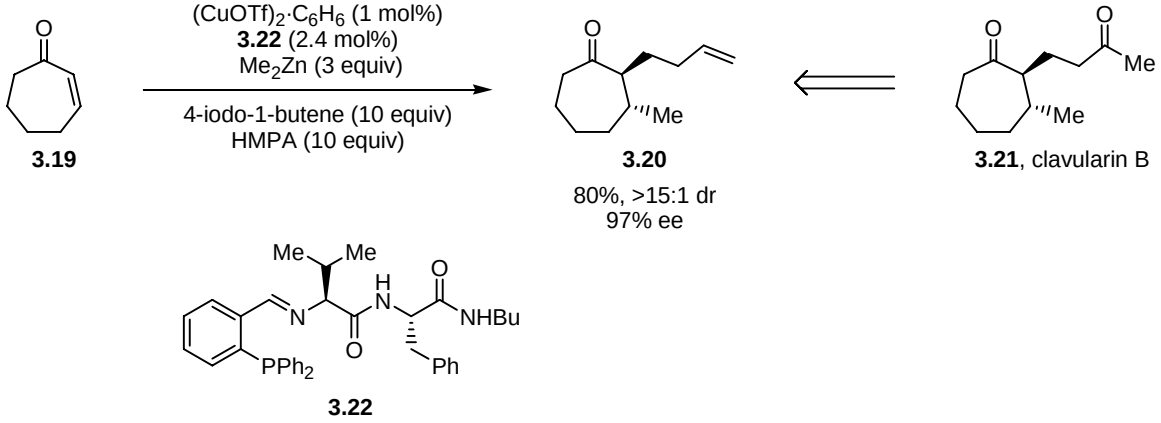
Scheme 3.5 Copper-catalyzed asymmetric intramolecular conjugate addition-aldol reaction

The zinc enolates generated *via* asymmetric conjugate addition of organozinc reagents to enones can be trapped by π-allyls obtained through palladium ionization of allylic acetate to provide 2,3-disubstituted enones **3.17** in good yields and excellent enantioselectivity (Scheme 3.6).[19] Feringa and co-worker subjected the product of this reaction to Wacker oxidation to obtain a ketone which was then subjected to base promoted annulation to afford bicyclic product **3.18**.



Scheme 3.6 Copper-catalyzed asymmetric conjugate addition-allylation reaction

Hoveyda and co-workers have developed peptide derived chiral ligand **3.22** for an asymmetric copper-catalyzed conjugate addition of dialkylzinc reagents to α,β-unsaturated carbonyl compounds in excellent yields and excellent enantioselectivity.[16] This asymmetric conjugate addition results in the generation of a zinc enolate, which can be trapped by alkyl halides and tosylates to provide products with contiguous stereocenters (Scheme 3.7). The use of the peptide-based chiral phosphine ligand has enabled functionalization of six, seven and the more challenging five membered cyclic enones in excellent enantioselectivity. This methodology has been applied in a concise total synthesis of anti-cancer clavularin B **3.21** in only four steps with 42% overall yield.[13b]

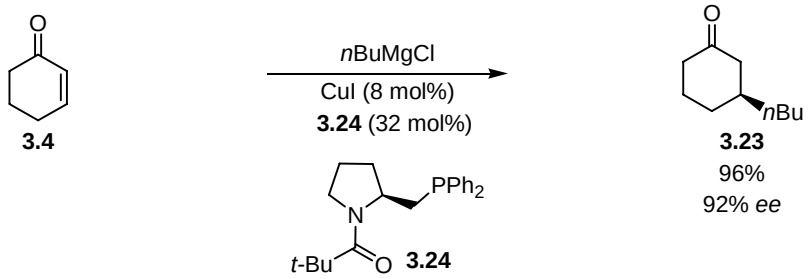


Scheme 3.7 Hoveyda's asymmetric Copper-catalyzed conjugate addition-alkylation reaction

3.2.3 Copper-Catalyzed Asymmetric Tandem Conjugate Addition-Electophilic Trapping Reactions Involving Grignard Reagents

Enantioselective conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds was the first asymmetric transformation to be studied.[20] This work

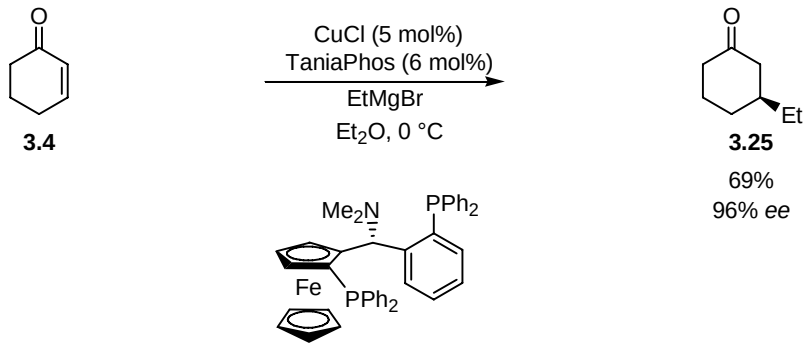
focused mainly on the chiral auxiliary approach, using readily available chiral alcohols, amines and thiols. In 1988, Lippard and co-workers reported the first enantioselective catalytic conjugate addition of Grignard reagents to enones using chiral amide ligands.[21] Subsequent to this seminal report several methods involving chiral thiolates[22] and chiral monophosphine[23] ligands were reported. However, enantioselectivities for these reactions rarely surpassed 90% *ee*. Tomioka's asymmetric conjugate addition of BuMgCl to cyclohexenone **3.4** using chiral amidophosphine (Scheme 3.8) [23c] and Sammakia's conjugate addition reaction that utilize chiral ferrocenyl monophosphine.[23d] are rare exceptions.



Scheme 3.8 Asymmetric conjugate addition of Grignard reagents to enones using amidophosphine **3.24**

The major problem limiting the development of highly enantioselective copper-catalyzed conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds is the competing uncatalyzed background reaction. Another challenge is stopping the competing 1,2-addition of the Grignard reagent to the carbonyl group. The advantage of using Grignard reagents over dialkylzinc reagents is that they are inexpensive, readily available and all the alkyl groups in the reagent can be transferred. In an effort to address these problems, Feringa and co-workers have developed a highly

enantioselective copper-catalyzed conjugate addition of Grignard reagents to enones and enoates with selectivity up to 98% ee using ferrocenyl diphosphine ligands (Scheme 3.9).[24] Trapping of the magnesium enolates generated *via* enantioselective copper-catalyzed conjugate addition to enones with reagents other than water is unknown. Herein we report the first enantioselective conjugate addition of Grignard reagents to cyclohexenone with subsequent electrophilic trapping of the resulting enolate with aryl groups from a bismuth(V) reagent



3.4

3.25

69%

96% *ee*

3.26 TaniaPhos

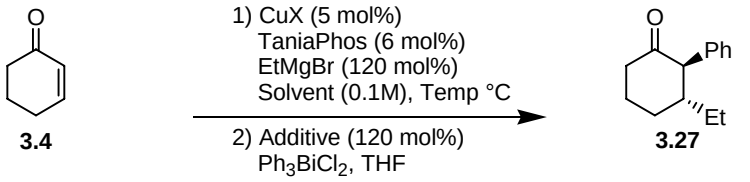
Scheme 3.9 Copper-catalyzed asymmetric conjugate addition on Grignard reagents to enones using ferrocenyl diphosphine ligands

3.3 Copper-Catalyzed Enantioselective Tandem Conjugate Addition of Grignard Reagents to Enones-Arylation Using Bismuth(V) Reagents

3.3.1 Optimization

Our studies began with examination of 2-cyclohexenone **3.4**. Exposure of **3.4** to EtMgBr (120 mol) in the presence of CuCl (5 mol%) and Taniaphos **3.26** (6 mol%) at 0 °C in Et_2O solvent (0.1 M), for 10 min, followed by addition of commercially available Ph_3BiCl_2 (150 mol%) in THF gave the product **3.27** in 10% isolated yield and 91% ee as a single stereoisomer as determined by ^1H NMR analysis (Table 3.1, entry 1). It was speculated that the magnesium enolate might aggregate in solution and thus addition of hexamethylphosphoramide (HMPA) would help break these aggregates increasing enolate reactivity. Gratifyingly, addition of HMPA (120 mol%) gave an increase in yield of **3.27** to 34% (Table 3.1, entry 2). Under identical conditions, but increasing the loading of Ph_3BiCl_2 from 150 mol% to 200 mol% the yield of **3.27** improved to 50% (Table 3.1, entry 3). A potential problem in this reaction is the competing 1,2-addition of the Grignard reagent to the enone. We speculated that decreasing the reaction temperature to -78 °C would slow down this competing pathway. Indeed, a decrease in temperature to -78 °C led to a 63% isolated yield of **3.27** (Table 3.1, entry 4). Performing the reaction in MeO^{t}Bu as a solvent gave **3.27** in 60% isolated yield and 96% ee (Table 3.1, entry 5). Finally by using CuBr•SMe_2 in place of CuCl we could obtain **3.27** in 62% yield and 96% ee. These reaction conditions represent our standard conditions for conjugate addition-arylation (Table 3.1, entry 6).

Table 3.1 Optimization for Copper-catalyzed enantioselective tandem conjugate addition-arylation of **3.4**



3.4 **3.27**

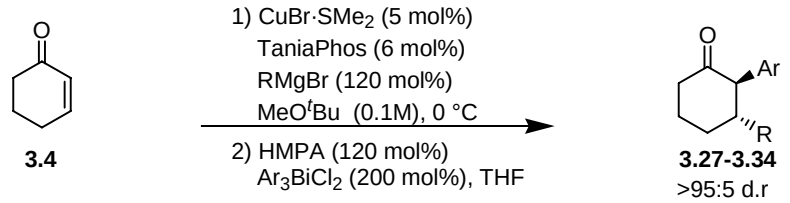
Entry	Solvent	CuX	Ph_3BiCl_2 (mol%)	Additive	Temp °C	%Yield	%ee
1	Et_2O	CuCl	150	-	0 °C	10	91
2	Et_2O	CuCl	150	HMPA	0 °C	34	90
3	Et_2O	CuCl	200	HMPA	0 °C	50	92
4	Et_2O	CuCl	200	HMPA	-78 °C	63	92
5	MeO^tBu	CuCl	200	HMPA	-78 °C	60	96
6	**MeO^tBu**	**$CuBr{\cdot}SMe_2$**	**200**	**HMPA**	**-78 °C**	**62**	**96**

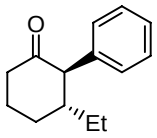
3.3.2 Substrate Scope

Under these standard conditions, the substrate scope of the tandem conjugate addition-arylation of enones reaction was explored. Enone **3.4** undergoes tandem conjugate addition of CH_3MgBr, EtMgBr, *n*-PrMgBr and *n*-BuMgBr with subsequent enolate arylation using Ph_3BiCl_2 to give products **3.27-3.30** in modest to good yields and excellent enantiomeric excess (Table 3.2). In each case, the products were obtained as single stereoisomer, as determined by ^1H NMR analysis. To further probe the scope of this transformation, triarylbismuth(V) dichlorides were prepared by first treating ArMgBr with $BiCl_3$ followed by oxidation of the resulting triarylbismuth(III) compound with sulfuryl chloride (SO_2Cl_2).[25] Tandem conjugate addition-arylation using para and meta

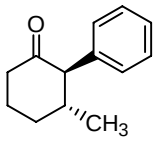
substituted triarylbismuth(V) dichlorides gave products **3.31-3.34** in modest yields and excellent enantiomeric excess (Table 3.2).

Table 3.2 Copper-catalyzed enantioselective tandem conjugate addition-arylation using bismuth(V) reagents.[a]

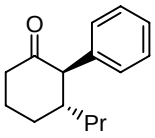




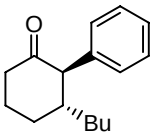
3.27, 62%
97% *ee*



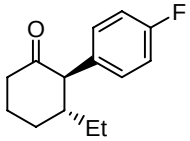
3.28, 59%
96% *ee*



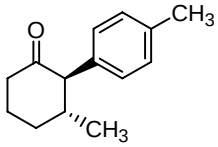
2.29, 53%
91% *ee*



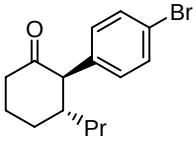
3.30, 58%
91% *ee*



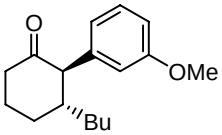
3.31, 60%
95% *ee*



3.32, 46%
90% *ee*



3.33, 49%
90% *ee*



3.34, 54%
91% *ee*

[a]Cited yields are of isolated material. In all cases, > 95:5 diasterioselectivity is observed

3.4 Summary and concluding remarks

In summary, we have developed a highly diastereo- and enantioselective method for vicinal difunctionalization of enones *via* tandem enantioselective conjugate addition-arylation using bismuth(V) reagents. To the best of our knowledge, this is the first example of tandem conjugate addition-arylation of enones using bismuth(V) reagents. The chemical yields for this reaction are modest due to competing polymerization and 1,2-addition to the carbonyl of the ketone, though we are able to perform a one pot difunctionalization which has been traditionally been restrained to two separate steps.

3.5 Experimental Section

General

All reactions were performed under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe. Flasks were flame-dried and cooled under argon. diethylether (Et_2O) was distilled from sodium/benzophenone ketyl. Dichloromethane (DCM) was distilled from calcium hydride. Hexamethylphosphoramide (HMPA) was distilled under reduced pressure from calcium hydride. Other solvents and chemical reagents obtained from commercial sources were used without further purification, unless otherwise noted. The known products **3.27, 3.28**,[26] **3.30**,[27] and **3.32**,[28] exhibited spectral data identical in all aspects as those reported in literature.

Analytical thin-layer chromatography (TLC) was carried out by using 0.2-mm commercial silica gel plates (DC-Fertigplatten Krieselgel 60 F_{254}, EMD Chemicals). Solvents for chromatography are listed as volume/volume ratios. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrometer. Samples were prepared as films through evaporation from dichloromethane or chloroform solution on sodium chloride plates. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 by using chemical ionization in the positive ionization mode. Accurate masses are reported for the molecular ion (M + 1) or a suitable fragment ion. Melting points were determined on a Thomas Hoover Uni-melt apparatus in open capillaries and are uncorrected.

Proton NMR (^{1}H NMR) spectra were recorded with a Varian Gemini (300 MHz) spectrometer, and Varian Gemini (400 MHz) spectrometer. Chemical shifts (δ) are

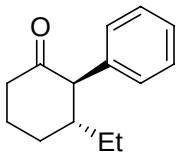
expressed as ppm relative to trimethylsilane (δ = 0.00 ppm), referenced to the residual protic solvent. Coupling constants are reported in Hertz. Carbon-13 NMR (^{13}C NMR) spectra were recorded on a Varian Gemini 300 (75 MHz) spectrometer, Varian Gemini 400 (100 MHz) spectrometer and Inova 500 (125 MHz) spectrometer. Chemical shifts (δ) are expressed as ppm relative to trimethylsilane (δ = 0.0 ppm), referenced to the center of the triplet at δ = 77.0 ppm for deuteriochloroform. ^{13}C NMR analyses were run routinely with broadband decoupling.

Representative procedure for the copper-catalyzed tandem enantioselective conjugate addition-arylation of enone 3.4

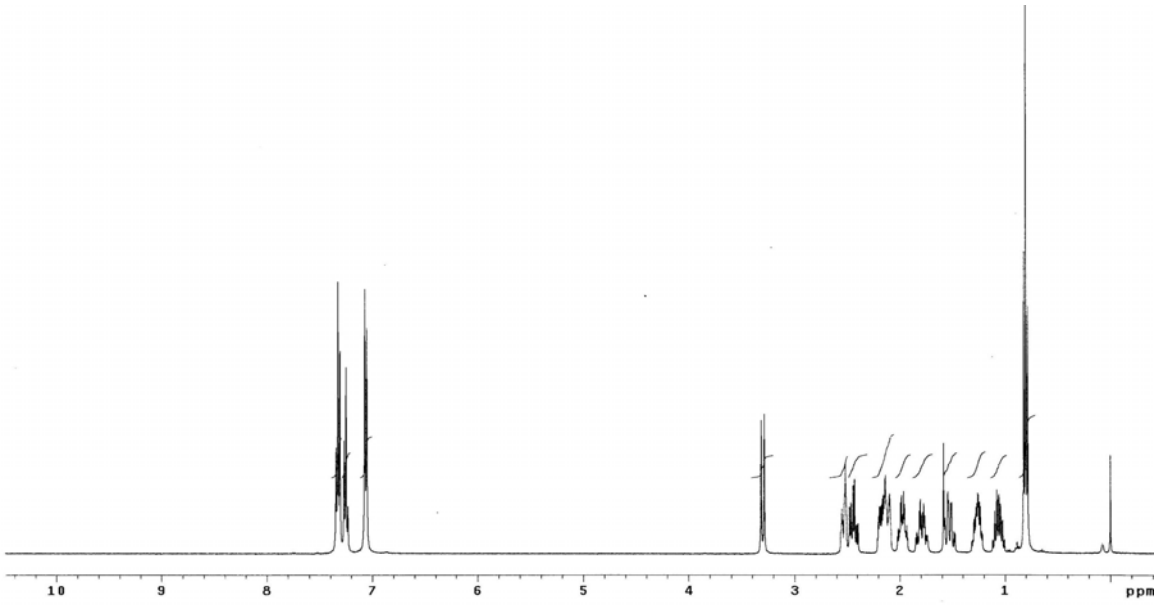
To a 10 mL round bottom flask charged with CuCl (0.01 mmol, 5 mol%) and Taniaphos (0.02 mmol, 6 mol%) was added Et_2O (2.5 mL, 0.1M). The suspension was stirred at 25 °C for 30 min. 2-Cyclohexenone **3.4** (0.31 mmol, 100 mol%) was added to the resulting homogenous solution and allowed to stir for an additional 10 min, after which the reaction vessel was cooled to -78 °C , EtMgBr (3M in Et_2O, 0.37 mmol, 120 mol%) was then added dropwise over 5 min. The reaction mixture was stirred for 1h at -78 °C, at which point HMPA (0.37 mmol, 120 mol%) and a solution of Ph_3BiCl_2 (0.62 mmol, 200 mol%) in THF (3 mL) were added. The stirring reaction mixture was removed from the cooling bath and allowed to warm to room temperature over a period of 3 h. A solution of 50 % aqueous Na_2CO_3 (3 mL) was added and allowed to stir for 10 min to convert excess Ph_3BiCl_2 to the more polar and insoluble Ph_3BiCO_3 for easy purification. The resulting mixture was filtered through celite, rinsing three times with Et_2O (5 mL). The filtrate was then extracted with Et_2O (3 X 5 mL), the combined organic extracts were

dried over $MgSO_4$, filtered and evaporated onto silica gel. Purification *via* column chromatography (SiO_2, 17:1 to 9:1 hexane/ethyl acetate) gives compound **3.27.**

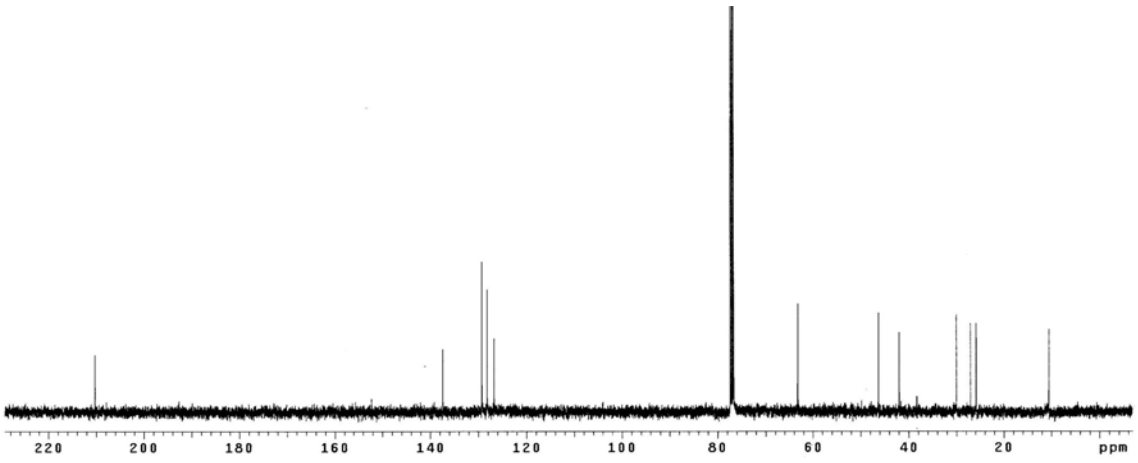
3.6 Spectroscopic Characterization Data



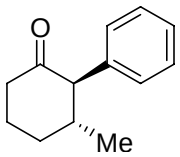
3-Ethyl-2-phenylcyclohexanone 3.27[26] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, *J* = 6.8 Hz, 2H), 7.25 (t, *J* = 6.8 Hz, 2H), 7.06 (d, *J* = 7.2 Hz, 1H), 3.30 (d, *J* = 11.6 Hz, 1H), 2.52 (m, 1H), 2.45 (td, *J* = 5.1, 13.1 Hz, 1H), 2.14 (m, 2H), 1.98 (m, 1H), 1.78 (qt, *J* = 3.8, 13.3 Hz, 1H), 1.52 (qd, *J* = 3.4, 13.0 Hz, 1H), 1.25 (m, 1H), 1.07 (hept, *J* = 7.2 Hz, 1H), 0.80 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.3, 137.4, 129.3, 128.2, 126.7, 63.3, 46.3, 41.9, 30.0, 27.1, 25.8, 10.5. Chiral HPLC: Daicel Chiralpak OD-H column, 95:5 hexanes:*i*-PrOH, λ = 254 nm, 0.5 mL/min, t_{major} = 14.48 min, t_{minor} = 15.79 min *ee* = 97%. $[\alpha]_D^{23}$ +80.4 °. (c =1 CH_2Cl_2)



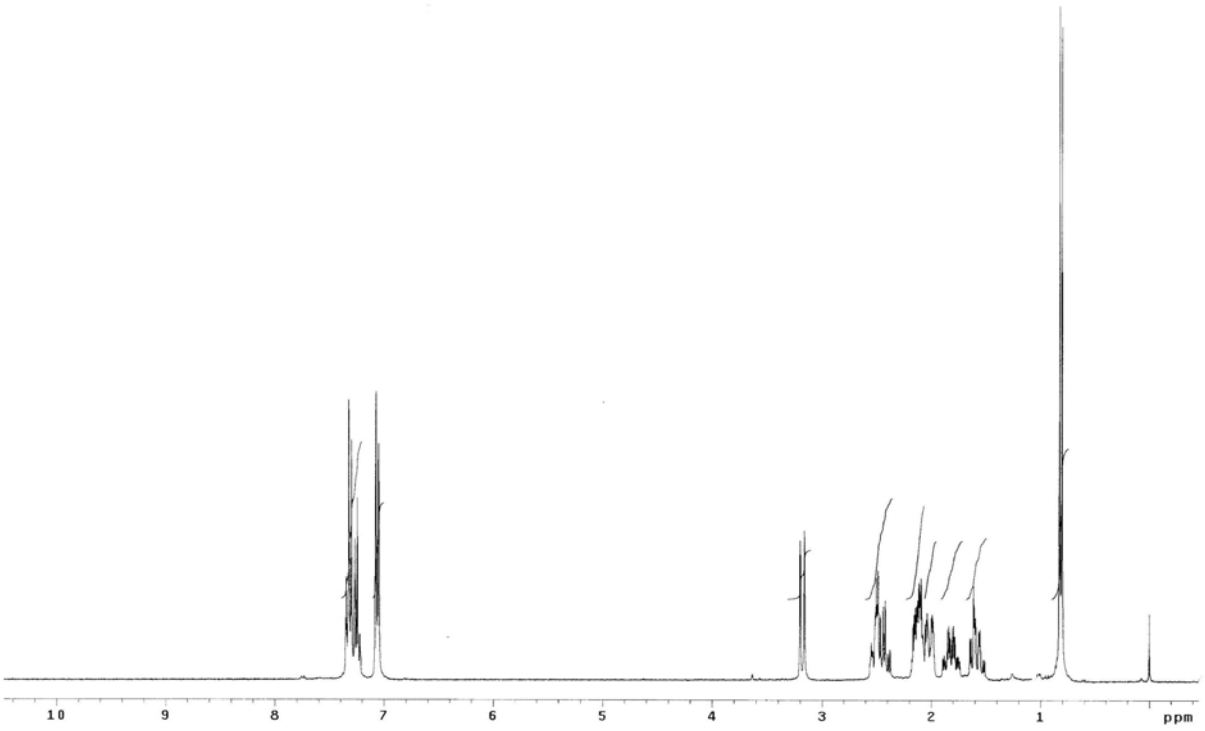
^{1}H NMR of **3.27**



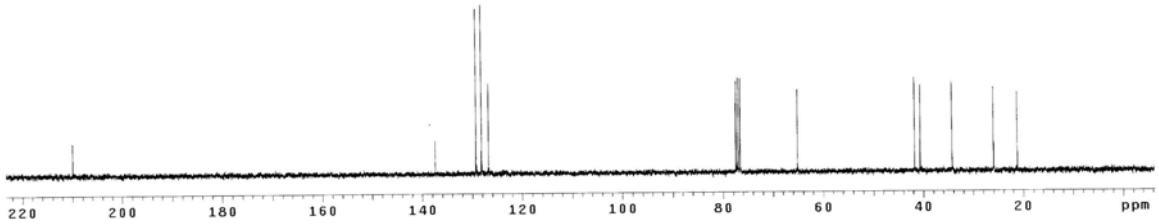
^{13}C NMR of **3.27**



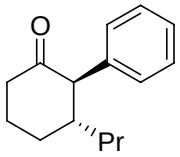
3-Metyl-2-phenylcyclohexanone 3.28[26] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 3H), 7.06 (d, *J* = 6.9 Hz, 2H), 3.18 (d, *J* = 11.5 Hz, 1H), 2.52 (m, 1H), 2.43 (qd, *J* = 6.9, 13.6 Hz, 1H), 2.14 (m, 2H), 2.01 (d, *J* = 14.9 Hz, 1H), 1.82 (qt, *J* = 4.6, 11.8 Hz, 1H), 1.59 (td, *J* = 3.6, 13.1 Hz, 1H), 0.80 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.9, 137.4, 129.2, 128.1, 126.7, 65.1, 41.7, 40.6, 34.2, 25.9, 21.2. Chiral HPLC: Daicel Chiralpak OD-H column, 95:5 hexanes:*i*-PrOH, λ = 254 nm, 0.5 mL/min, t_{major} = 14.48 min, t_{minor} = 15.79 min *ee* = 95%. $[\alpha]_D^{23}$ +75° (c = 0.4 CH_2Cl_2).



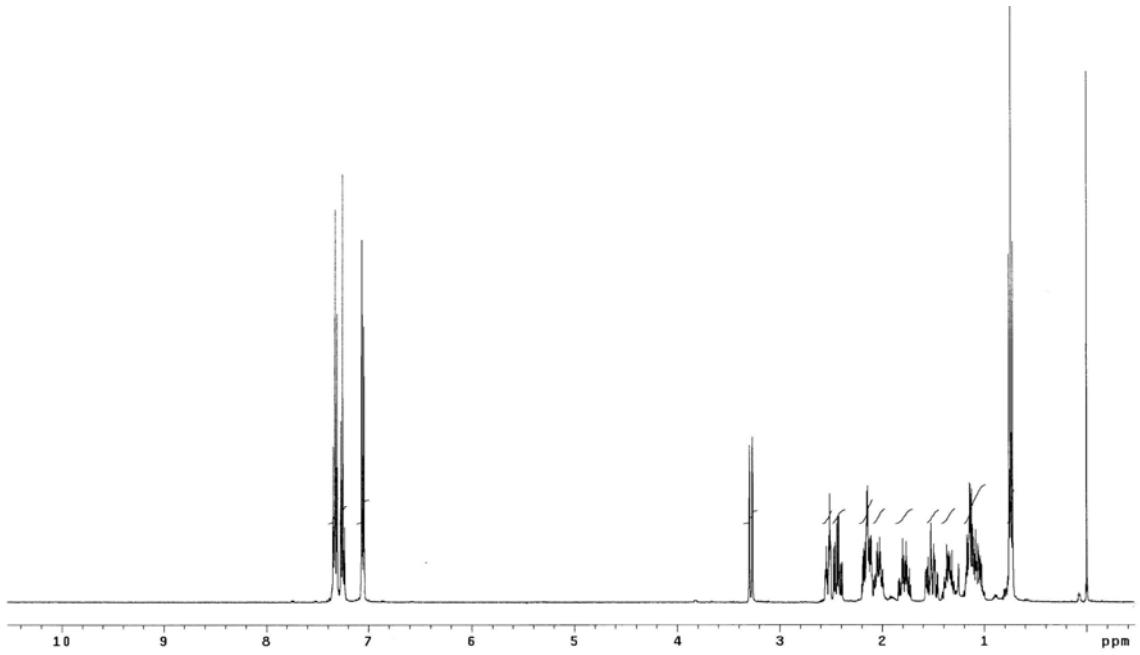
^{1}H NMR of **3.28**



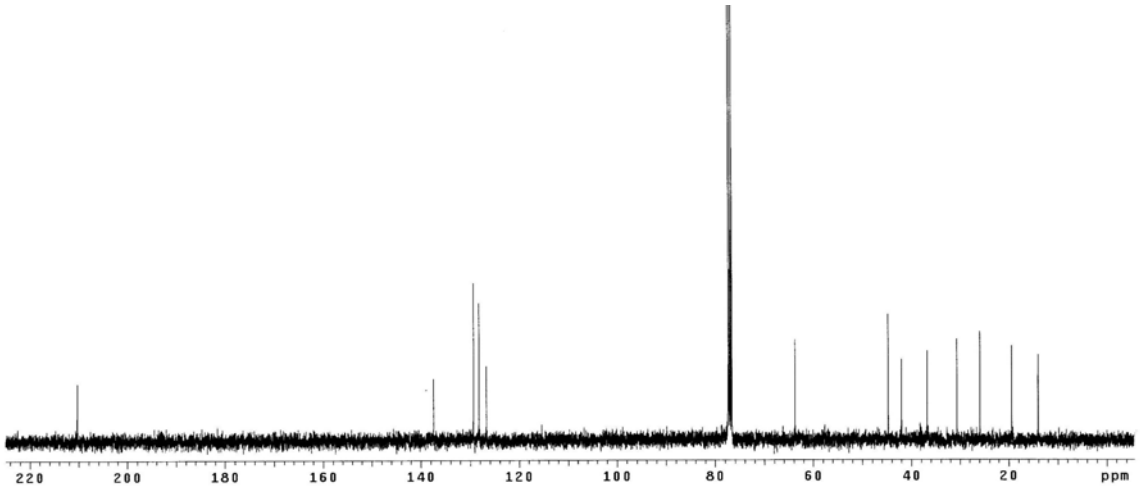
^{13}C NMR of **3.28**



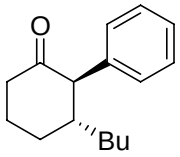
2-Phenyl-3-propylcyclohexanone 3.29 ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, *J* = 6.8 Hz, 2H), 7.25 (t, *J* = 5.8 Hz, 1H), 7.05 (d, *J* = 6.8 Hz, 2H) 3.27 (d, *J* = 11.3 Hz, 1H), 2.52 (m, 1H), 2.44 (qdd, *J* = 1.0, 5.8, 13.7 Hz, 1H), 2.14 (m, 2H), 2.04 (m, 1H), 1.78 (qt, *J* = 4.4, 14.0 Hz, 1H), 1.50 (qd, *J* = 3.4, 13.0 Hz, 1H), 1.35 (m, 1H), 1.11(m, 3H), 0.74 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.3, 137.4, 129.3, 128.2, 126.7, 63.7, 44.7, 41.9, 36.8, 30.6, 25.9, 19.4, 14.0. FTIR (NaCl): 3019, 2948, 2857, 1712, 1496, 1452, 1313, 1176, 745, 698, 556 cm^{-1}. HRMS: calcd for $C_{15}H_{21}O$ [M+1] 217.1592 found 217.1591. Chiral HPLC: Daicel Chiralpak OD-H column, 95:5 hexanes:*i*-PrOH, λ = 254 nm, 0.5 mL/min, t_{major} = 13.04 min, t_{minor} = 14.73 min *ee* = 91%. $[\alpha]_D^{23}$ +100 °. (c = 0.5 CH_2Cl_2)



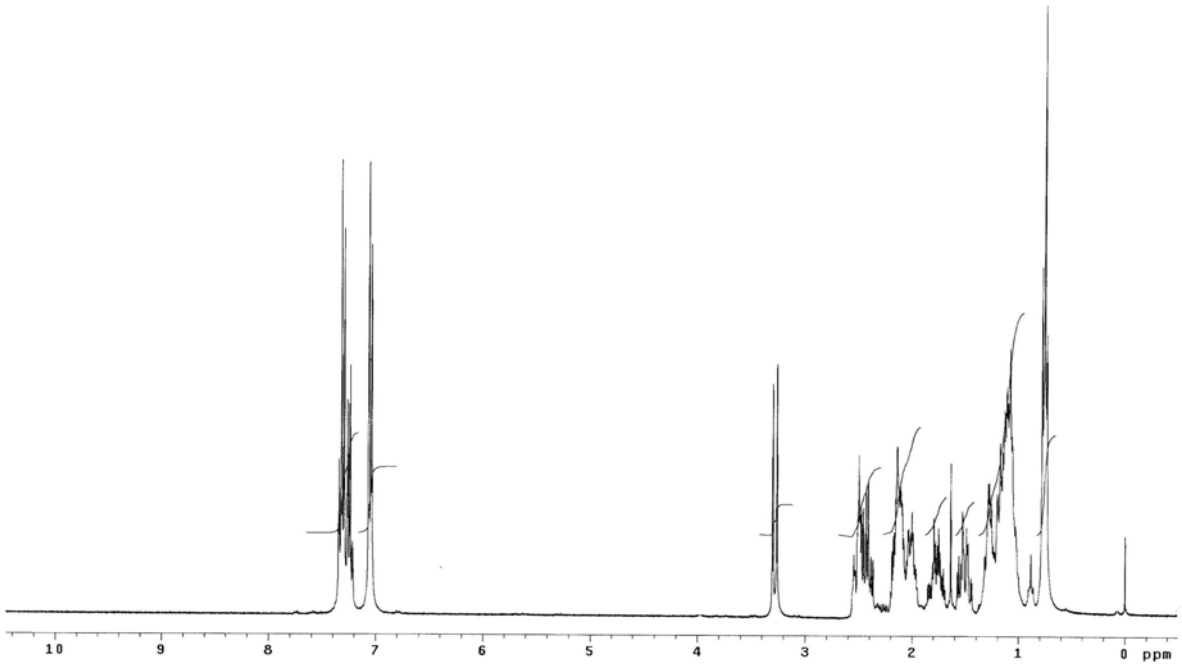
^{1}H NMR of **3.29**



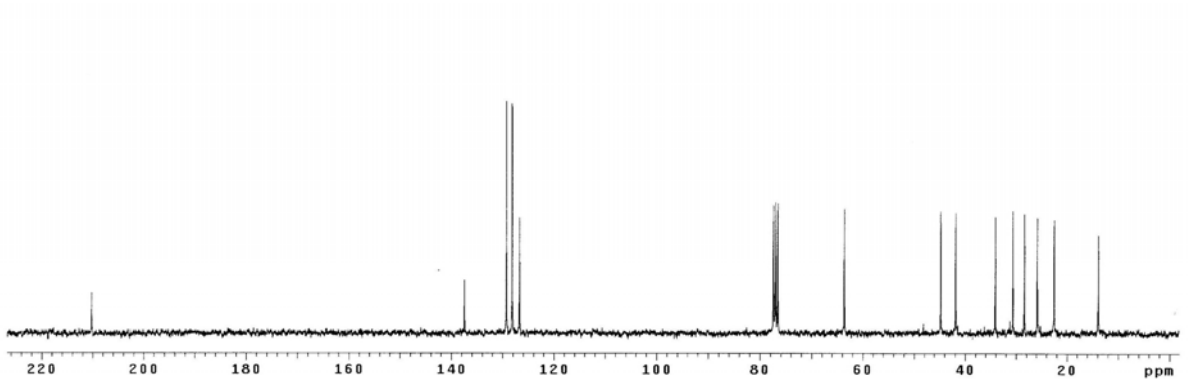
^{13}C NMR of **3.29**



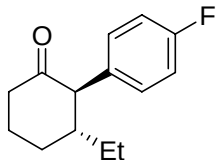
3-Butyl-2-phenylcyclohexanone 3.30[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (t, *J* = 7.1 Hz, 2H), 7.24 (d, *J* = 7.0 Hz, 1H), 7.05 (d, *J* = 6.6 Hz, 2H) 3.28 (d, *J* = 11.3 Hz, 1H), 2.51 (m, 1H), 2.46 (qd, *J* = 5.8, 13.4 Hz, 1H), 2.08 (m, 2H), 1.78 (m, 1H), 1.53 (m, 1H), 1.24 (m, 6H), 1.08 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.3, 137.4, 129.3, 128.1, 126.7, 63.6, 44.8, 41.9, 34.1, 30.6, 28.4, 25.8, 22.5, 13.9. Chiral HPLC: Daicel Chiralpak OD-H column, 95:5 hexanes:*i*-PrOH, λ = 254 nm, 0.5 mL/min, t_{major} = 12.57 min, t_{minor} = 14.00 min *ee* = 91%. $[\alpha]_D^{21}$ +93.7 ° (c = 0.8 CH_2Cl_2).



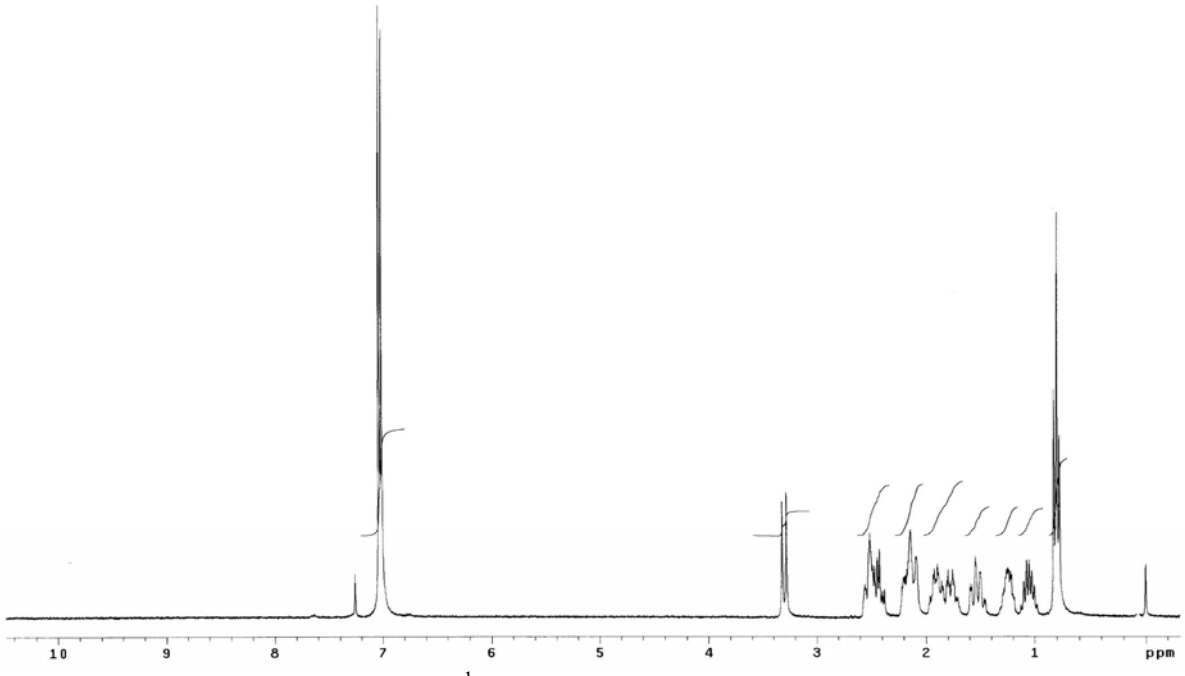
^{1}H NMR of **3.30**



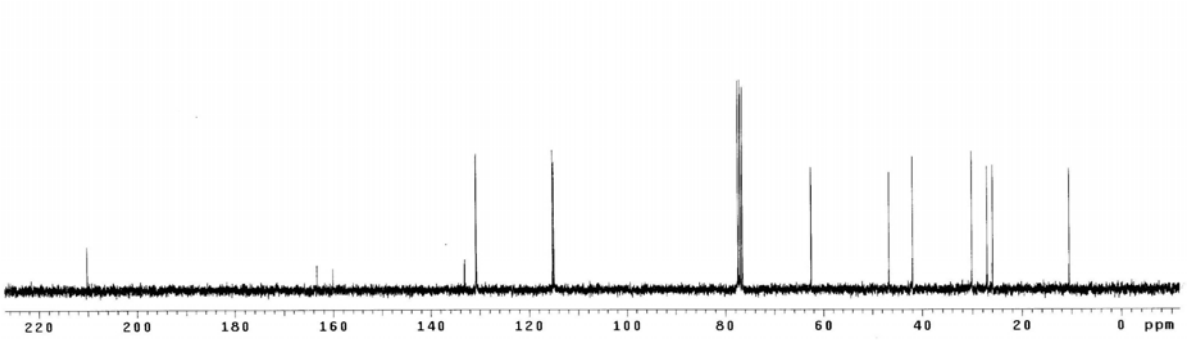
^{13}C NMR of **3.30**



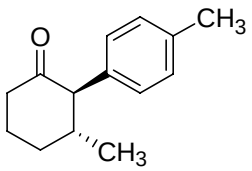
3-Ethyl-2-(4-fluorophenyl)cyclohexanone 3.31 ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, *J* = 7.2 Hz, 4H), 3.30 (d, *J* = 12.0 Hz, 1H), 2.51 (m, 1H), 2.41 (td, *J* = 6.4, 13.8 Hz, 1H), 2.14 (m, 2H), 1.92 (m, 1H), 1.76 (dt, *J* = 3.3, 13.0 Hz, 1H), 1.54 (q, *J* = 13.5 Hz, 1H), 1.25 (m, 1H), 1.06 (quint, *J* = 7.2 Hz, 1H), 0.80 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.1, 161.7 (d, *J* = 144 Hz) 133.0, 130.6 (d, *J* = 7.7 Hz), 115.1 (d, *J* = 21.4 Hz), 62.5, 46.6, 41.9, 30.1, 27.0, 25.9, 10.4. FTIR (NaCl): 2962, 2934, 2864, 1712, 1602, 1509, 1456, 1221, 1178, 1158, 822 cm^{-1}. HRMS: calcd for $C_{14}H_{18}OF$ [M+1] 221.1342 found 221.1344. Chiral HPLC: Daicel Chiralpak OD-H column, 99:1 hexanes:*i*-PrOH, λ = 254 nm, 0.5 mL/min, t_{major} = 16.17 min, t_{minor} = 16.58 min *ee* = 95%. $[\alpha]_D^{23}$ +40.1 ° (c = 0.75 CH_2Cl_2)



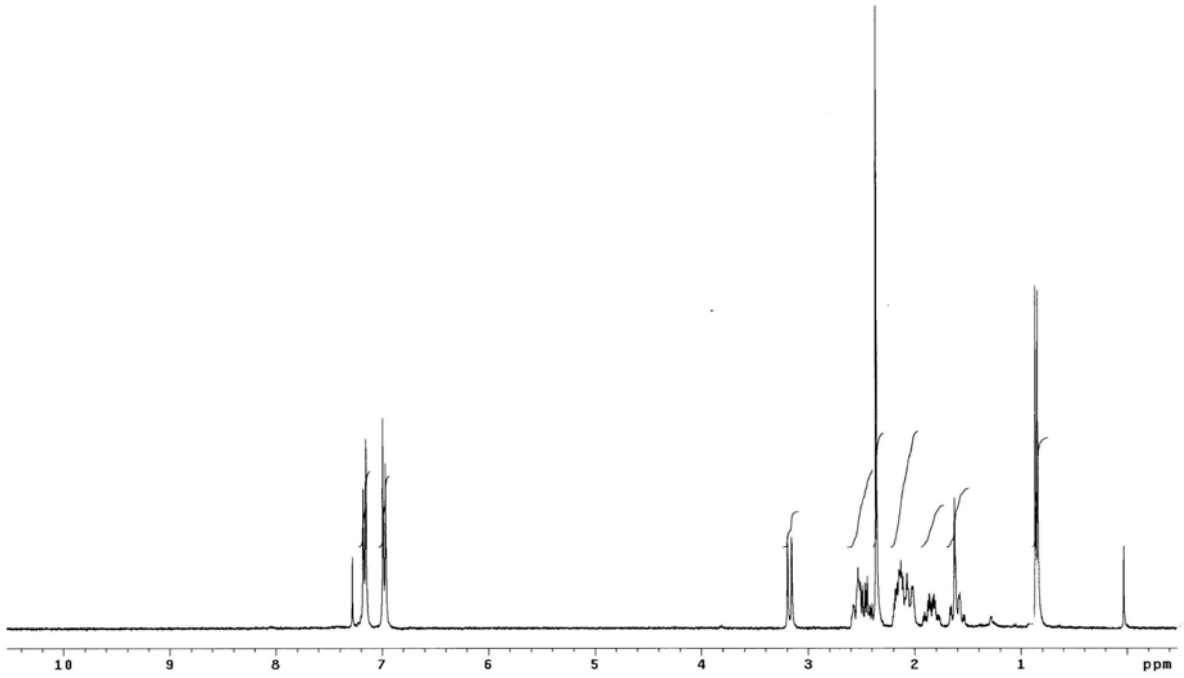
^{1}H NMR of **3.31**



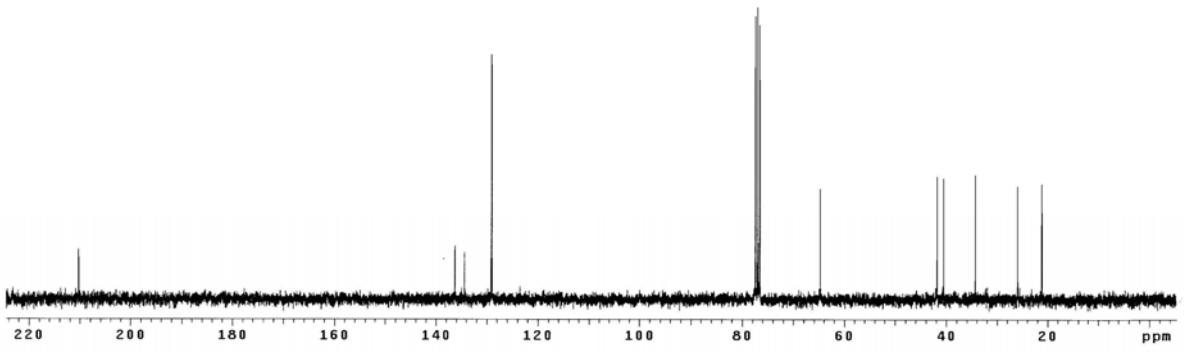
^{13}C NMR of **3.31**



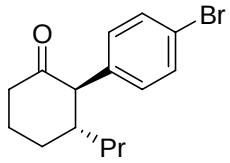
3.Methyl-2-p-tolylcyclohexanone 3.32[28] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (t, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 3.18 (d, *J* = 11.5 Hz, 1H), 2.52 (m, 1H), 2.46 (qd, *J* = 5.9, 13.7 Hz, 1H), 2.36 (s, 3H), 2.10 (m, 3H), 1.85 (qt, *J* = 3.6, 13.3 Hz, 1H), 1.62 (qd, *J* = 3.3, 12.5 Hz, 1H), 0.85 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.2, 136.3, 134.3, 129.1, 129.0, 64.7, 41.8, 40.5, 34.3, 25.9, 21.2, 21.1. Chiral HPLC: Daicel Chiralpak OD-H column, 95:5 hexanes:*i*-PrOH, λ = 254 nm, 0.5 mL/min, t_{major} = 12.89 min, t_{minor} = 13.86 min *ee* = 91%. $[\alpha]_D^{21}$ +27 ° (c = 0.73 CH_2Cl_2)



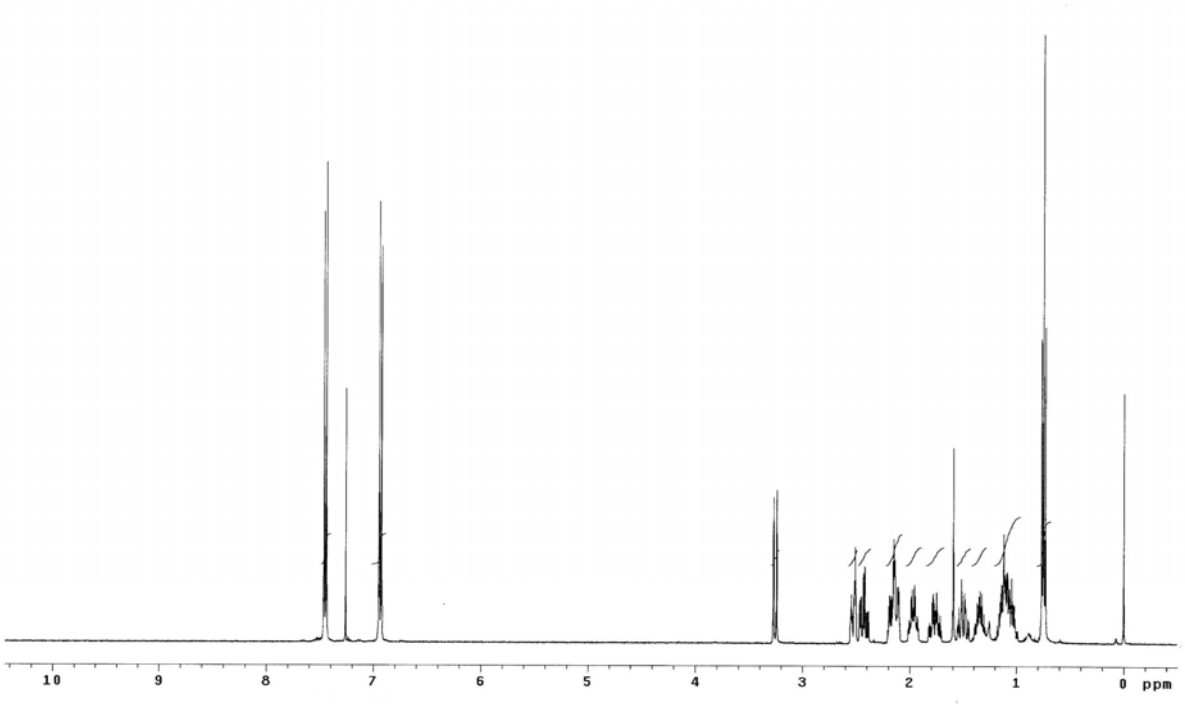
^{1}H NMR of **3.32**



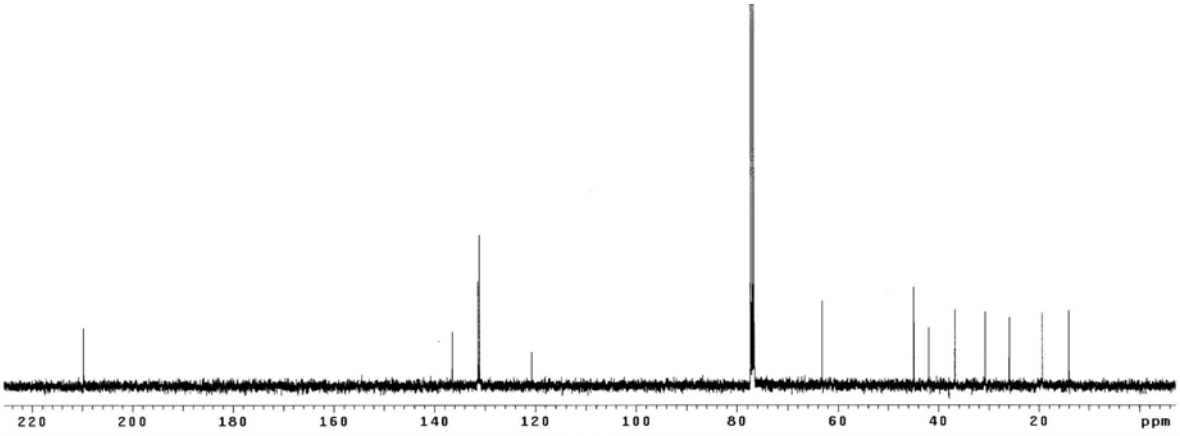
^{13}C NMR of **3.32**



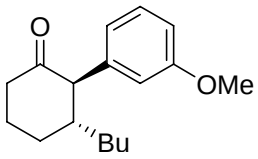
2-(4-Bromophenyl)-3-propylcyclohexanone 3.33 ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 3.26 (d, *J* = 11.6 Hz, 1H), 2.52 (m, 1H), 2.43 (tdd, *J* = 1.0, 6.2, 13.7 Hz, 1H), 2.14 (m, 2H), 1.96 (m, 1H), 1.78 (qt, *J* = 4.1, 13.0 Hz, 1H), 1.49 (q, *J* = 11.3 Hz, 1H), 1.34 (m, 1H), 1.10 (m, 3H), 0.75 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.8, 136.4, 131.3, 131.0, 120.7, 63.2, 44.9, 41.9, 36.7, 30.7, 25.9, 19.3, 14.0. FTIR (NaCl): 2954, 2931, 2848, 1713, 1478, 1454, 1407, 1172, 1067, 1002, 802 cm^{-1}. HRMS: calcd for $C_{15}H_{20}O$ [M+1] 295.0698 found 295.0702. Chiral HPLC: Daicel Chiralpak OD-H column, 95:5 hexanes:*i*-PrOH, λ = 254 nm, 0.5 mL/min, t_{major} = 11.42 min, t_{minor} = 12.70 min *ee* = 90%. $[\alpha]_D^{23}$ +46 ° (c = 0.76 CH_2Cl_2).



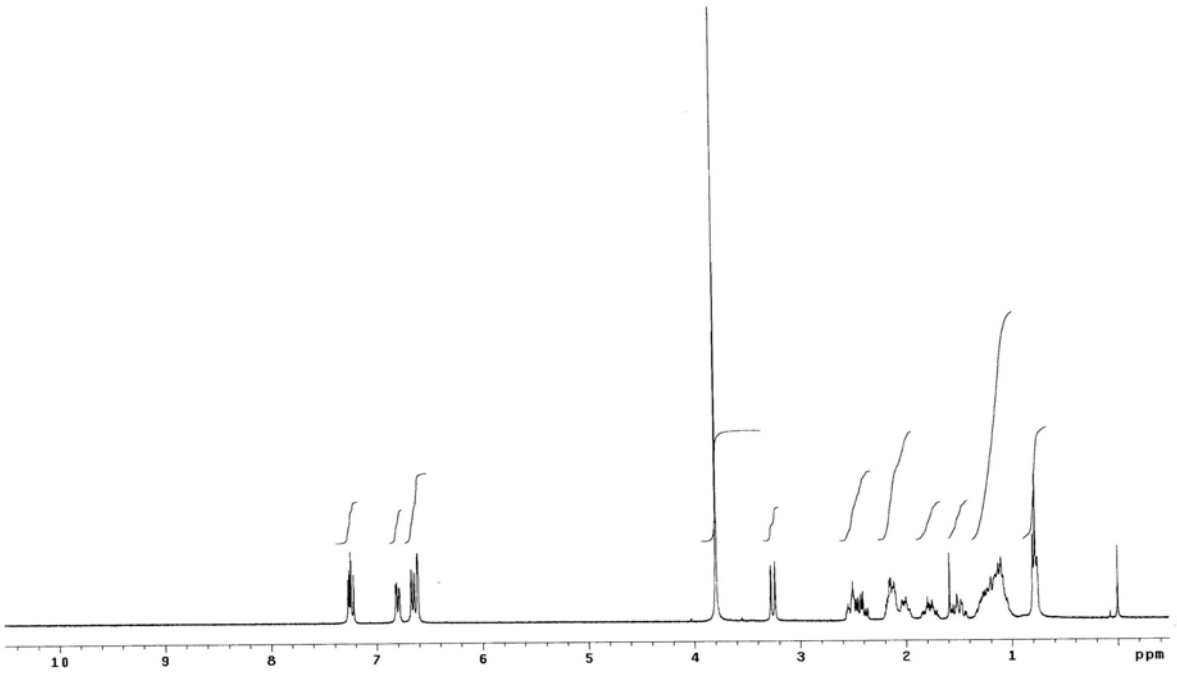
^{1}H NMR of **3.33**



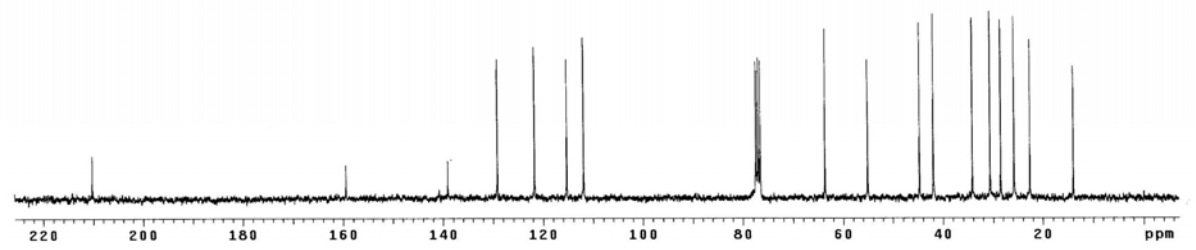
^{13}C NMR of **3.33**



3-Butyl-2-(3-methoxyphenyl)cylohexanone 3.34. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (t, *J* = 7.8 Hz, 1H), 6.81 (dd, *J* = 1.8, 7.6 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.61 (s, 1H), 3.79 (s, 3H), 3.25 (d, *J* = 8.1 Hz, 1H), 2.51 (m, 1H), 2.42 (td, *J* = 5.8, 13.3 Hz, 1H), 2.10 (m, 3H), 1.78 (m, 1H), 1.53 (q, *J* = 10.7 Hz, 1H), 1.20 (m, 6H), 0.78 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.2, 159.4, 139.0, 129.1, 121.7, 115.3, 111.9, 63.7, 55.1, 44.7, 41.9, 34.1, 30.6, 28.5, 25.8, 22.6, 13.9. FTIR (NaCl): 2931, 2849, 1713, 1596, 1578, 1484, 1454, 1290, 1255, 1161, 1043, 767, 691 cm^{-1}. HRMS: calculated [M+1] for $C_{17}H_{25}O_2$ 261.1855 found 261.1856. Chiral HPLC: Daicel Chiralpak OD-H column, 95:5 hexanes:*i*-PrOH, λ = 254 nm, 0.5 mL/min, t_{major} = 16.64 min, t_{minor} = 20.25 min *ee* = 91%. $[\alpha]_D^{22}$ +40 °. (c =1 CH_2Cl_2).



^{1}H NMR of **3.34**



^{13}C NMR of **3.34**

3.7 References

[1] For selected reviews on tandem or "domino" transformations, see: (a) Guo, H.-C.; Ma, J.-A. *Angew. Chem. Int. Ed.* **2006**, *45*, 354. (b) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (d) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed.* **1993**, *32*, 131.

[2] For selected reviews on stoichiometric conjugate addition-electrophilic trapping, see: (a) Suzuki, M.; Noyori, R. *Organocopper Reagents* **1994**, 185. (b) Taylor, R. J. K. *Synthesis* **1985**, 364. (c) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38,* 225. (d) Ihara, M.; Fukumoto, K. *Angew, Chem. Int. Ed. Engl.* **1993**, *32,* 1010.

[3] Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308.

[4] Stork, G. *Pure Appl. Chem*. **1968**, *17*, 383.

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Chapter 4 Hydrogen Mediated Catalytic Addition of Metallo-Aldehyde Enolates to Ketones

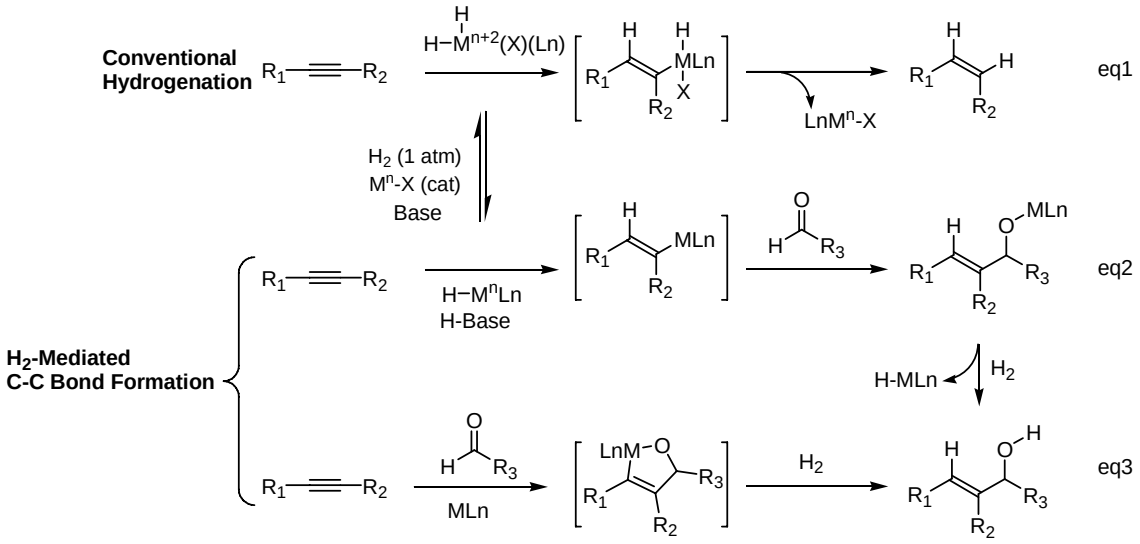
4.1 Introduction

Hydrogenation is the most cost effective and atom economical process, however it is limited to simple reduction of unsaturated π-systems.[1] Few hydrogenation reactions have been utilized in the context of C-C bond formation: they include hydroformylation,[2] Fischer-Tropsch-type reactions[3] and other C-C bond forming reactions.[4] Many reductive C-C bond forming reactions involve stoichiometric reductants such as silane, borane, alane and stannane. These reactions often generate stoichiometric byproducts of which some are toxic. Conversely hydrogenative C-C bond formations are environmentally benign, atom economical, and cost efficient because stoichoimetric byproducts are not generated. Inspired by the profound impact of these reactions the Krische group became interested in developing general methods for hydrogenative C-C bond forming reactions.

4.1.1 Mechanistic Features

In the conventional hydrogenation the mechanism involves a dihydrido metal complex that hydrometallates the alkyne or alkene to give a organomonohydrido metal complex intermediate (Scheme 4.1, eq 1). For C-C bond formation to occur capture of this organomonohydrido metal intermediate is necessary, however this is not possible due to rapid C-H reductive elimination. Based on Schrock and Osborn studies on hydrogenation using cationic rhodium complexes the dihydrido ($Rh^{III}H_2LnX$) and the monohydrido rhodium ($Rh^{I}HLn$) complexes exist in equilibrium in the presence of an exogenous base.[5] The use of a mild base generates monohydrido metal complex, this

could extend the lifetime of the hydrometallated intermediates since it lacks an appendant hydride, thus C-C bond formation is possible (Scheme 4.1, eq 2). An alternative pathway involves oxidative coupling to furnish a metallocyle which is known in other rhodium catalyzed couplings (Scheme 4.1, eq 3).[6] In this pathway C-C bond formation precedes hydrogen activation to form the metallocycle, subsequent σ-bond metathesis with hydrogen provides the C-C bond formation product. On the basis of these mechanistic hypotheses the Krische group has developed a family of catalytic hydrogen mediated C-C bond forming reactions. The focus of this chapter is to give an overview of the reductive aldol reactions developed in our group and detail my contribution to this area.



Scheme 4.1 A plausible mechanism for hydrogenative C-C bond formation

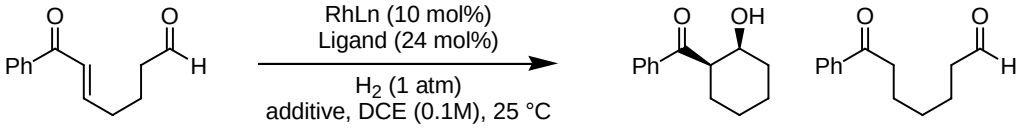
4.1.2 Reductive Aldol Under Hydrogenation Conditions

4.1.2.1 Rh-Catalyzed Hydrogenative Aldol Using Aldehyde Acceptors

Predicated on the mechanistic hypothesis described in section 4.1.1 the Krische group has developed a rhodium catalyzed hydrogen mediated aldol reaction.[7] To assess the feasibility of this hydrogen mediated reductive aldol reaction, an intramolecular system was designed that contains a phenyl-substituted monoenone monoaldehyde. Exposure of this substrate to $Rh(COD)_2OTf$ (10 mol%) and PPh_3 (24 mol%), under atmosphere of hydrogen, provided the aldol cyclization product in 21% with concomitant formation of simple alkene reduction products (Table 4.1, entry 1). On the basis of Schrock and Osborn's[5] observation that addition of base facilitates the deprotonation of $LnRh^{III}(H_2)X$ to form $Rh^{I}HLn$ which would circumvent competing simple reduction, KOAc was added. Gratifyingly the yield of the desired products was improved dramatically (Table 4.1, entry 2). Additionally, electron-deficient phosphine ligands like $(p\text{-}CF_3Ph)_3P$ improved the partitioning between aldol products and conjugate reduction products (Table 4.1, entry 4). This was rationalized by invoking and intramolecular co-ordination of the metal complex to the aldehyde, thus increasing its electrophilicity. Notably, neutral rhodium complexes such as Wilkinson's catalyst provided low yields of the aldol product with substantial quantities of conjugate reduction product (Table 4.1, entry 5). Control experiments were performed to rule out the possibility of a tandem conjugate reduction-base aided aldol reaction. The product of conjugate reduction was subjected to the reaction conditions and no product was obtained. Also this transformation does not proceed *via* Morita-Baylis-Hilman reaction since no cyclization

product was obtained in the absence of hydrogen. The *syn*-diastereoselectivity can be accounted for by a Zimmerman-Traxler type transition state assuming the formation of a *Z*-enolate. Aromatic, heteroaromatic, and aliphatic monoenone monoaldehyde substrates participate in this transformation.

Table 4.1 Rh-catalyzed reductive cyclization of monoenone monoaldehyde **4.1a**



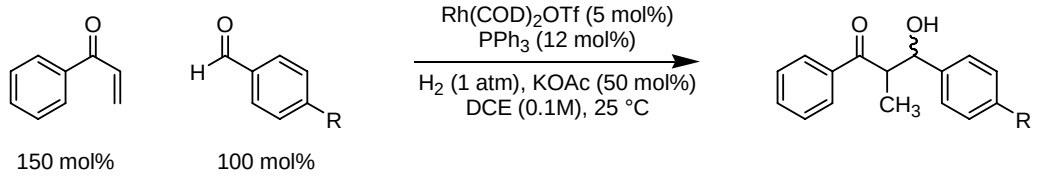
4.1a **4.1b** **4.1c**

Entry	RhLn	Ligand	Additive (mol%)	*Syn*-(*Anti*-aldol)	Conjugate Reduction
1	$Rh(COD)_2OTf$	PPh_3	----	21% (0%)	25%
2	$Rh(COD)_2OTf$	PPh_3	KOAc (30%)	58% (1%)	21%
3	$Rh(COD)_2OTf$	$(p\text{-}CF_3Ph)_3P$	----	53% (4%)	22%
4	$Rh(COD)_2OTf$	$(p\text{-}CF_3Ph)_3P$	KOAc (30%)	80% (9%)	0.1%
5	$Rh(PPh_3)_3Cl$	----[-]	KOAc (30%)	1% (0%)	59%

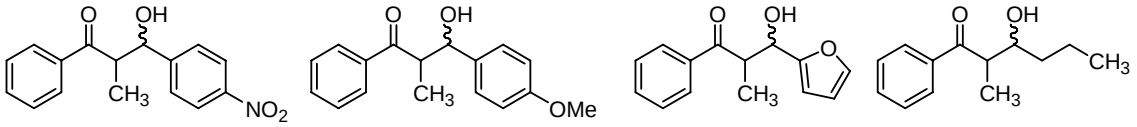
An intermolecular variant of this transformation has been developed through adjustment of the reaction conditions (Table 4.2). Here two equivalent of the enone, $Rh(COD)_2OTf$ (5 mol%), PPh_3 (12 mol%), and KOAc (50 mol%) in an atmosphere of hydrogen provide reductive aldol products in good yield with modest diastereoselectivity. By using tri-2-furylphophosphine modified rhodium catalysts the diastereoselectivity of the reductive aldol reaction was improved tremendously (Table 4.3). [8] The diastereoselectivities observed in this reaction at ambient temperature and pressure are comparable to those achieved in related aldol reaction at low-temperature using alkali enolates. [9] This remarkable diastereoselectivity is attributed to π-acidic ligand tri-2-

furphosphine which renders the rhodium center Lewis acidic resulting in a tighter Zimmerman-Traxler type transition state.

Table 4.2 Intermolecular reductive aldol reaction under hydrogenation conditions



150 mol% 100 mol%



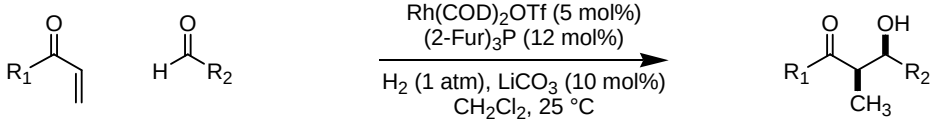
4.2
92%, (1.8 :1) (syn:anti)

4.3
75%, (1.7 :1)

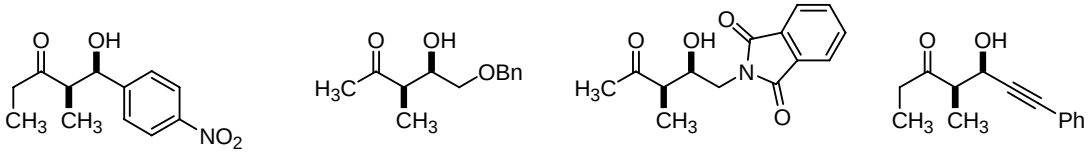
4.4
92%, (2.5 :1)

4.5
44%, (2 :1)

Table 4.3 Highly s*yn*-selective reductive aldol through tri-2-furylphosphine effect



150 mol% 100 mol%



4.6
90%, 25 :1 dr

4.7
90%, 17 :1 dr

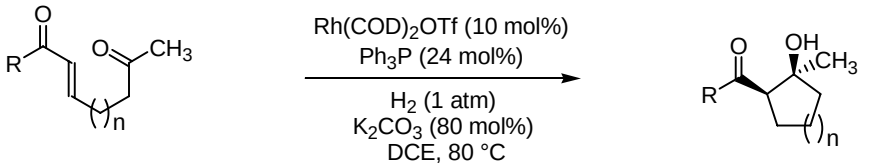
4.8
95%, 50 :1 dr

4.9
70%, 10 :1 dr

4.1.2.2 Rh-Catalyzed Hydrogenative Aldol Using Ketone Acceptors

Having developed the Rh-catalyzed hydrogenative aldol reaction involving aldehyde acceptors, the methodology was then extended to other electrophilic partners

such as ketones. Whereas similar aldol reactions using ketone acceptors are known,[10] it was anticipated that conjugate reduction would predominate over reductive aldol due to the reduced electrophilicity of the ketones compared to the aldehydes. Rh-catalyzed reductive aldol of monoenone mono ketone substrates performed at elevated temperature (80 °C) provided the desired aldol products in good yields and excellent diastereoselectivity along with products of conjugate reduction Scheme 4.2.[11]



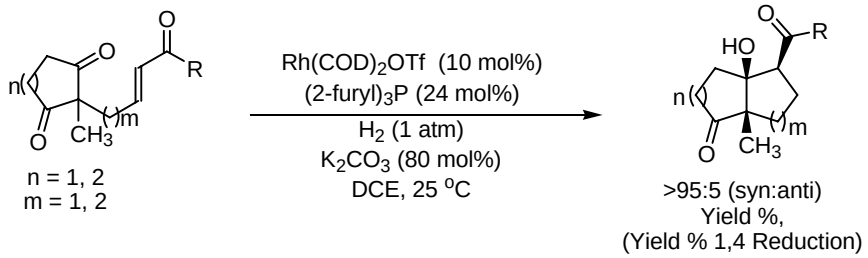
n = 1, 2
R = Ph, Ar, Het-Ar

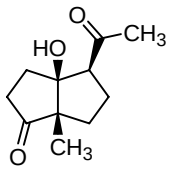
66-83% Aldol Product
(8-24% 1,4-Reduction
95:5 d.r

Scheme 4.2 Rh-catalyzed hydrogenative aldol using ketone acceptors

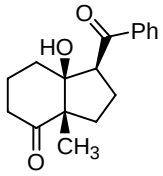
It was possible to attenuate formation of the undesired conjugate reduction product by using a more electrophilic dione acceptors. The dione acceptors are more reactive due to the inductive effect and also the relief of dipole-dipole interaction after reaction. Monoenone with appendant dione substrates undergo hydrogenative reductive aldol at ambient temperature to provide bicyclic products as single diastereomers (Scheme 4.4). Here five and six membered ring formation is achieved setting 3 contiguous stereocenters, of which two are quaternary, in a single manipulation.The conjugate addition products were not observed, with exception of the strained *cis*-decalone **4.13.**

Table 4.4 Rh-catalyzed hydrogenative aldol using dione acceptors

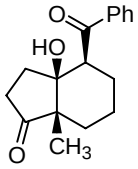




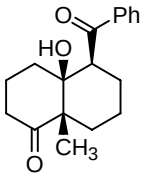
4.10
88%
(0%)



4.11
73%
(0%)



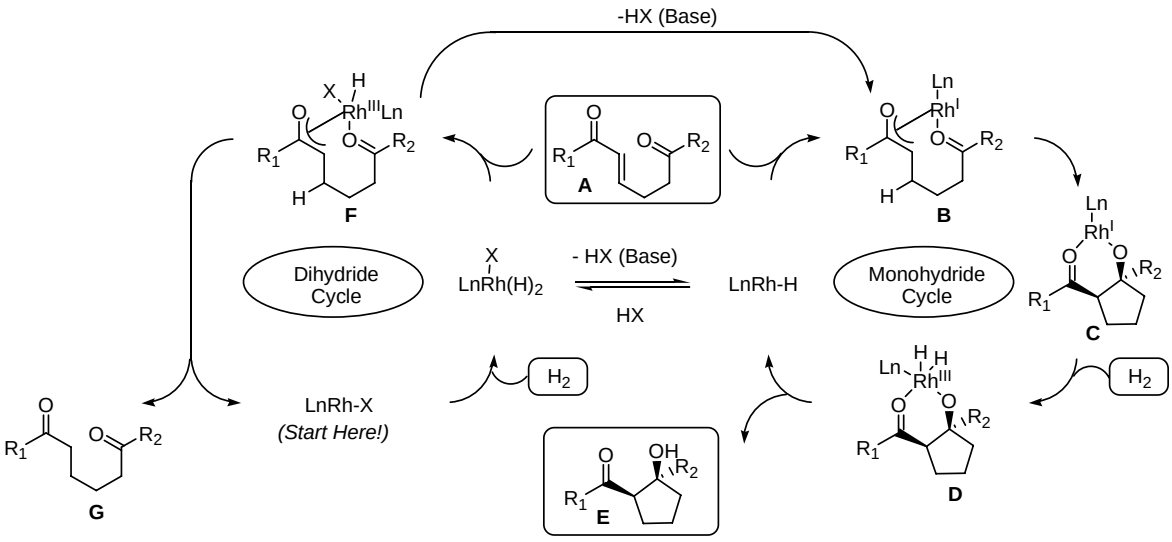
4.12
63%
(0%)



4.13
65%
(15%)

Based on deuterium labeling experiments, ESI-MS data and control experiments a plausible catalytic cycle was proposed (Scheme 4.3).[12] Starting with oxidative addition of molecular hydrogen to cationic rhodium complex $LnRh^{I}X$ generates dihydridorhodium(III) complex $LnRh^{III}(H_2)X$. Due to its enhanced acidity,[13] it can be deprotonated by an exogenous base to afford a monohydride complex $LnRh^{I}H$. These complexes are in equilibrium[5] leading to two possible catalytic cycles: the monohydride catalytic cycle starts with hydrometallation of the enone **A** by $LnRh^{I}H$ to give the rhodhium (I) enolate **B,** which can undergo electrophilic trapping by the appendant ketone or aldehyde to yield the aldolate **C** (Scheme 4.3). The rhodium(I) aldolate **C** undergoes hydrogen oxidative addition to give the dihydrido rhodium(III) aldolate **D** which reductively eliminates to afford the aldol product **E**. The dihydride cycle involves $LnRh^{III}(H_2)X$ which hydrometallates the enone **A** to yield LnRh(III)(alkyl)(hydrido)

enolate intermediate **F.** which can undergo either alkyl-hydrogen reductive elimination to give the undesired conjugate reduction product **G** or in the presence of exogenous base the LnRh(III)(alkyl)(hydrido) enolate **F** can be deprotonated to yield the rhodhium(I) enolate **B**, which shifts the catalytic cycle to the monohydride cycle



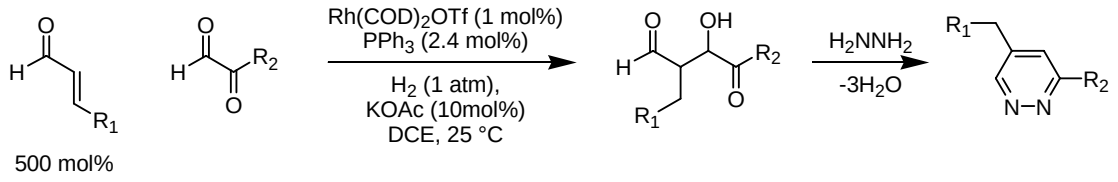
Scheme 4.3 A plausible catalytic mechanism for hydrogenative aldol reaction

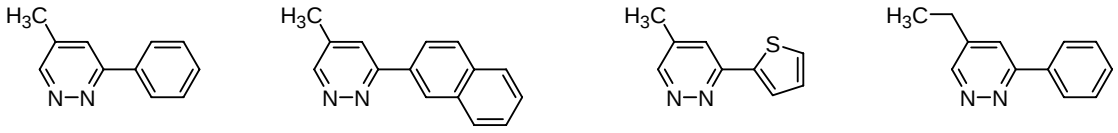
4.1.2.3 Rh-Catalyzed Hydrogenative Generation of Metallo-Aldehyde Enolates *via* Enal Hydrogenation.

The utility of metallo-aldehyde enolates in the context of an aldol reaction is complicated by the formation of products that derive from polyaldolization, dehydration, and Tischenko-type reaction.[14] Catalytic aldolizations using aldehyde enolates have been achieved indirectly through preformed enol silane, or *via* imminium ion-enamine catalysis.[15] Given the mild conditions of the Rh-catalyzed reductive aldol reaction, Krische and co-workers have shown that this method can be used to generate metallo-

aldehyde enolates which are subsequently trapped by glyoxals (Table 4.5).[16] The aldol products (β-hydroxy aldehydes) were not stable and therefore derivatization *in situ* to the corresponding pyridazine by adding methanolic hydrazine was performed. Coupling of acrolein and crotonaldehyde to a variety of aromatic and heroaromatic glyoxals is achieved under Rh-catalyzed hydrogenative reductive aldol conditions. Although the chemical yields are modest, this transformation represents a novel method for synthesis of pyridazine rings.

Table 4.5 Rh-catalyzed hydrogenative aldol condensation to pyridazines





4.14
62%

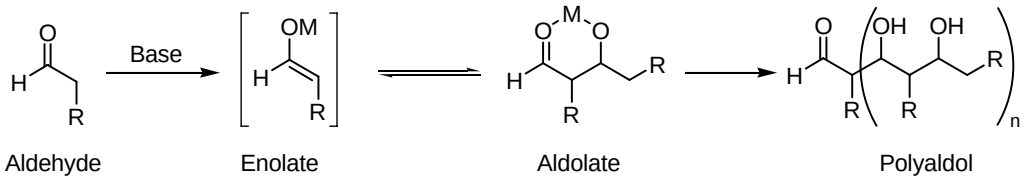
4.15
59%

4.16
31%

4.17
47%

4.2 Catalytic Addition of Metallo-Aldehyde Enolates to Ketones

Catalytic direct addition of metallo-aldehyde enolates to ketones is, to the best of our knowledge, unprecedented. Although a stoichiometric method to accomplish these aldolizations was reported by Oshima.[17] The primary issues limiting the utility of metallo-aldehyde enolates in cross-aldolizations with ketone partners are polyaldolization at the stage of enolate formation and the diminished thermodynamic driving force. According to the Ab initio calculations by Oshima, the formation of 3-hydroxyaldehyde ($(CH_3)_2CH(OH)CH_2CHO$ from acetone and acetaldehyde has a formation energy of 21.155 kcal/mol, whereas the formation of 3-hydroxyketone ($CH_3CH(OH)CH_2COCH_3$) is exothermic with a formation energy of -10.455 kcal/mol. When generating alkali enolates from aldehydes polyaldolization is a big problem. For example if an aldehyde is treated with a base to form an enolate, as soon as this enolate is formed it will react with another molecule of the aldehyde to give an aldolate (Scheme 4.4). This aldolate contains a reactive aldehyde moiety which can react with another enolate, this process repeats to provide the polyaldol.



Scheme 4.4 Polyaldolization during enolate generation

Inspired by the mild conditions for the intra- and intermolecular aldolization of enone pronucleophiles with glyoxals, aldehyde, and ketone acceptors[7-8, 11,16] we directed our efforts to a more challenging variant: the cross-aldol reaction between aldehydes

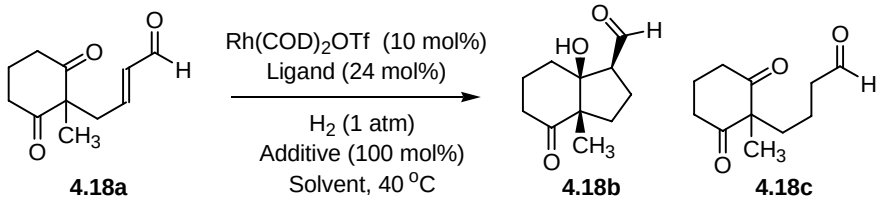
enolates and ketones under hydrogenation conditions. Herein, we report an intramolecular catalytic cross-aldol cyclization of keto-enals under hydrogenation conditions.[18]

4.2.1 Optimization

To explore the viability of the catalytic addition of metallo-aldehyde enolates to ketones, keto-enal substrate **4.18a** (Table 4.6) was synthesized *via* allylation of 2-methyl-1,3-cyclohexanedione, followed by cross metathesis of the allylated product with acrolein using Grubbs second generation catalyst. Exposure of **4.18a** to $Rh^{I}(COD)_2OTf$ (10 mol%), PPh_3 (24 mol%), and KOAc, (100 mol%) in dichloroethane (DCE) at 40 ^{o}C under an atmosphere of hydrogen (1 atm) gave the aldol product **4.18b** in 23% yield, accompanied by a 50% yield of the simple conjugate reduction product **4.18c** (Table 4.6, entry 1). Based on the mechanism, we speculated that the use of a stronger base could generate a Rh(I) enolate from Rh(III)(hydrido)-enolate thus shifting the mechanism to the monohydride catalytic cycle resulting in an increase in the desired aldol product. Accordingly, upon substituting potassium carbonate for potassium acetate the yield of **4.18b** increased to 40% (Table 4.6 entry 2). It was speculated that under dilute conditions polyaldolization associated with aldehyde enolates would be minimized. Indeed under more dilute conditions, **4.18b** is obtained in 59% yield (Table 4.6, entry 3). Under identical conditions, but changing the solvent to THF the yield of **4.18b** is increased to 65% (Table 4.6, entry 4). Finally, using a more electron deficient phosphine ligands, **4.18b** is obtained in greater than 70% yield (Table 4.6, entries 5 and 6). All reactions were run at 40 °C, attempts to perform the reactions at room temperature caused

increased reaction time and diminished yields. These conditions were applied to other substrates to afford both 5- and 6- membered aldol cyclization products (Table 4.7).

Table 4.6 Optimization of the catalytic aldol cycloreduction of keto-enal **4.18a**



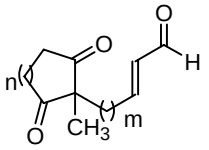
4.18a **4.18b** **4.18c**

Entry	Ligand	Additive	Solvent (conc.)	Yield 4.18b	Yield 4.18c
1	Ph_3P	KOAc	DCE (0.1 M)	23%	(50%)
2	Ph_3P	K_2CO_3	DCE (0.1 M)	40%	(28%)
3	Ph_3P	K_2CO_3	DCE (0.05 M)	59%	(29%)
4	Ph_3P	K_2CO_3	THF (0.05 M)	65%	(32%)
5	$(p\text{-}CF_3Ph)_3P$	K_2CO_3	THF (0.05 M)	72%	(22%)
6	**$(2\text{-furyl})_3P$**	**K_2CO_3**	**THF (0.05 M)**	**73%**	**(21%)**

4.2.2 Substrate Scope

Under our standard conditions aldol cycloreduction proceeds well to provide 5-membered bicyclic aldol products **4.18b** and **4.19b** in 72% and 73% yield, accompanied by 16% and 21% of 1,4 reduction products respectively. As illustrated by substrates **4.20a** and **4.21a**, cyclization to form 6-membered rings occurs in slightly diminished yields due to increased levels of conjugate reduction products. Here, aldol reaction provides products **4.20b** and **4.21b** in 63% and 59% yields with 1,4 reduction products in 30% and 29% respectively. The structural assignment of **4.18b** and **4.21b** were corroborated by single crystal x-ray diffraction analysis (Figure 4,1 and 4.2). The major diastereomer in both cases is the *syn*-aldol product.

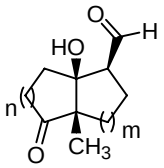
Table 4.7 Catalytic aldol cycloredution of keto-enals **4.18a-4.21a**



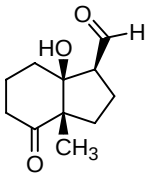
4.18a, n = 2, m = 1
4.19a, n = 1, m = 1
4.20a, n = 1, m = 2
4.21a, n = 2, m = 2

$Rh(COD)_2OTf$ (10 mol%)
$(2\text{-furyl})_3P$ (24 mol%)

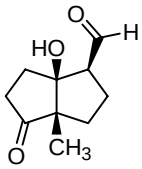
H_2 (1 atm)
K_2CO_3 (100 mol%)
THF, 40 ^oC



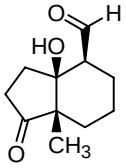
4.18b-4.21b, Yield %, syn:anti,
4.18c-4.21c, (Yield % 1,4 Reduction)



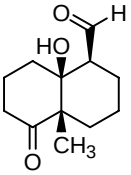
4.18b, 73%, 10:1
4.18c, (21%)



4.19b, 72%, 2:1
4.19c, (16%)



4.20b, 63%, 5:1
4.20c, (30%)



4.21b, 59%, 4:1
4.21c, (29%)

Figure 1 Relative stereochemistry as determined by single X-ray diffraction analysis for acid derivative of **4.18b**

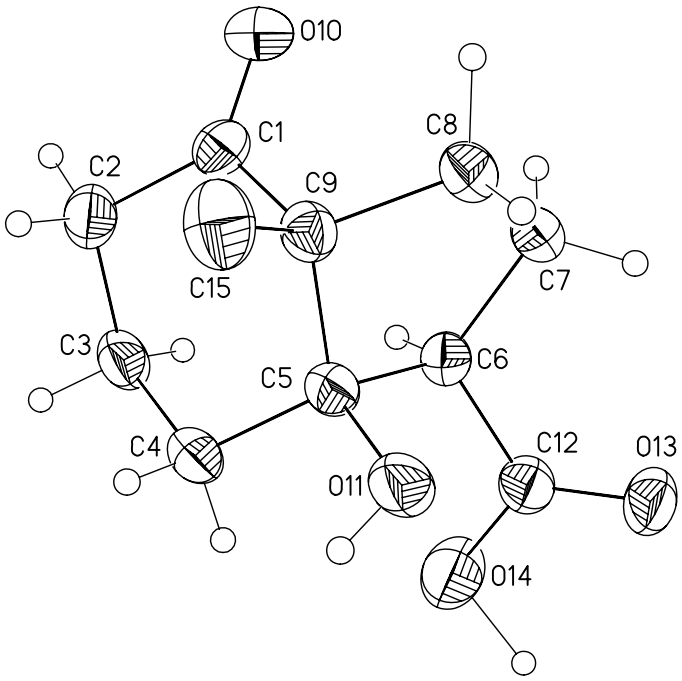
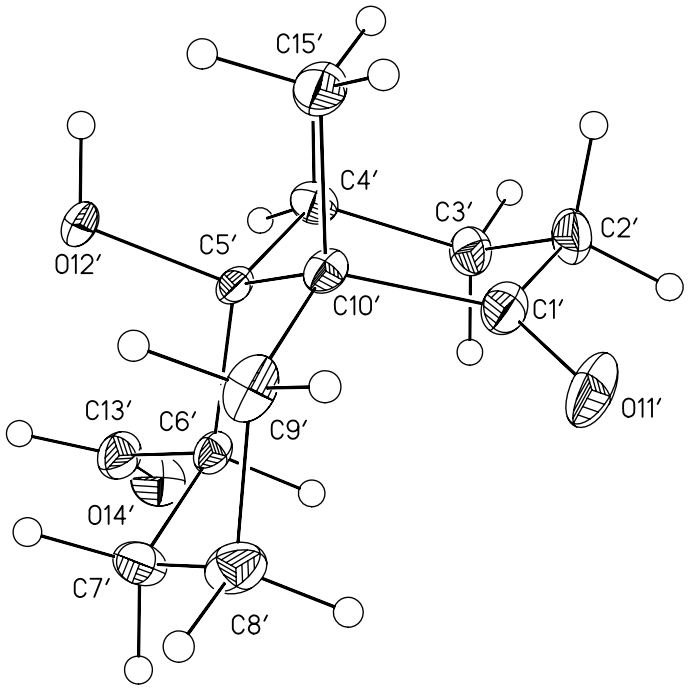
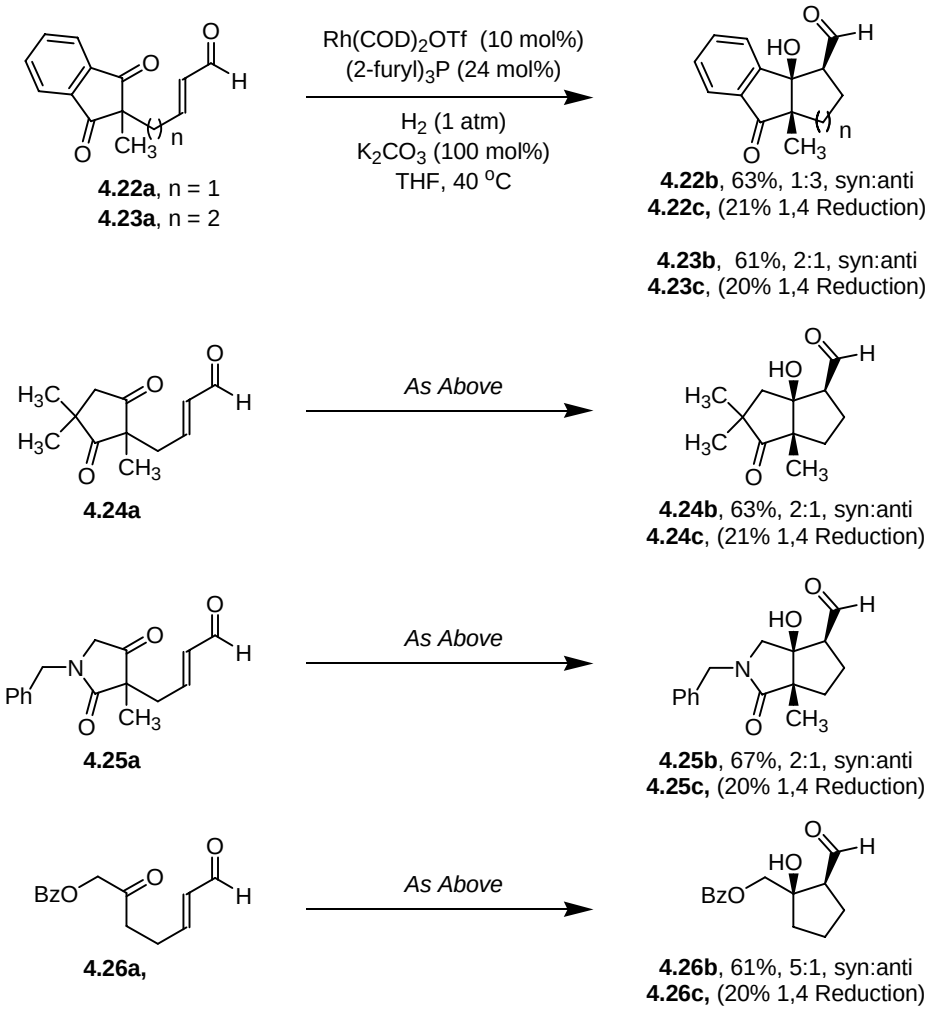


Figure 2 Relative stereochemistry as determined by single X-ray diffraction analysis of product **4.21b**



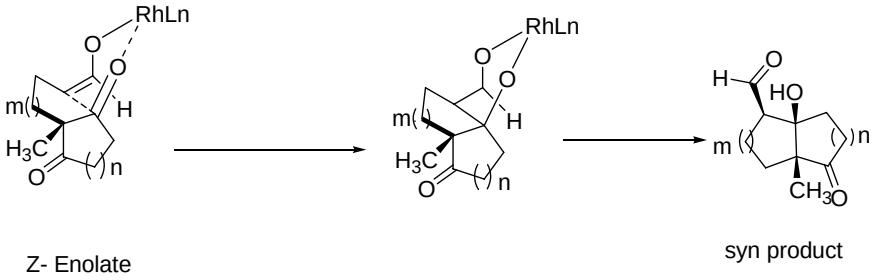
To expand the substrate scope of this new variant of catalytic aldol reaction, we explored other substrates (Scheme 4.5). Substrates **4.22a** and **4.23a** undergo cycloreduction to furnish aldol products **4.22b** and **4.23b** in moderate yields, these examples demonstrate that aromatic ketones are viable electrophilic partners in this transformation. The relative stereochemistry of the *syn*-aldol major product in **4.22b** was confirmed by NOE experiments. Keto-enals **4.24a** and **4.25a** highlight the chemoselectivity of this aldolization reaction when non symmetrical ketones acceptors are used. For **4.24a** the geminal dimethyl substitution makes one of the ketones sterically encumbered and thus the less sterically hindered ketone undergoes aldol cyclization. In

substrate **4.25a** cyclization occurs onto the ketone and not the *N*-benzyl amide. Notably hydrogenolytic cleavage of *N*-benzyl amide is not observed. Monoenal monoketone substrate **4.26a** undergoes reductive aldol cyclization efficiently, relative to the 1,3-dione substrates which are more electrophilic.



Scheme 4.5 Catalytic aldol cycloredution of keto-enals **4.22a-4.26a**

The observed *syn*-aldol stereochemistry of the product in this reaction can be rationalized by invoking a Zimmerman-Traxler transition state and the intermediacy of a (*Z*)-enolate (Scheme 10). The anti-aldol products observed could be attributed to isomerization of the enolates from (*Z*)-enolate to (*E*)-enolates. The modest *syn*:*anti* ratios are consistent with lack of selectivity inherent to aldol additions employing aldehyde enolates.[19] This methodology is the first example of catalytic addition of metallo-aldehyde enolates to ketones under hydrogenation conditions.



Z- Enolate

syn product

Scheme 4.6 Transition state model consistent with observed stereochemistry

4.3 Summary and Concluding Remarks

We have developed the first example of catalytic direct cross-aldolization of metallo-aldehyde enolates with ketones under hydrogenation conditions. These results and those previously studied in our group, involving catalytic hydrogen-mediated reductive coupling of enones to carbonyl acceptors support the feasibility of developing a broad class of catalytic C-C bond forming reactions using our enone-electrophile template. This catalytic cross-aldolization of aldehyde enolates with ketones still require some improvement, since the aldol products are formed in modest diastereoselectivity and are accompanied by simple reduction products. Future work will be devoted to the design of a catalyst system that would address these problems.

4.4 Experimental Section

General

All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe. Flasks were flame-dried and cooled under a stream of argon. Dichloroethane was distilled from calcium hydride. Tetrahydrofuran was distilled from sodium and benzophenone. Acrolein was dried over magnesiun sulfate and then distilled under argon atmosphere. The acid derived from **4.18b** was prepared via Jones oxidation of **4.18b**.[20]

Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Krieselgel 60 F_{254}). Preparative column chromatography employing silica gel was performed according to the method of Still.[21] Solvents for chromatography are listed as volume/volume ratios. Melting points were determined on a Thomas-Hoover melting point apparatus in a sealed tube. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/e (relative intensity). Accurate masses are reported for the molecular ion (M+1) or a suitable fragment ion.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (300 MHz) spectrometer, a Mercury (400 MHz) spectrometer and an Inova (500 MHz) spectrometer. Chemical Shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a

Varian Gemini 300 (75 MHz) spectrometer, a Mercury 400 (100 MHz) spectrometer and an Inova 500 (125 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the center of the triplet at 77.00 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadbrand decoupling.

Representative Procedure for the Synthesis of Substrates 4.18a, 4.19a, 4.22a, 4.24a, 4.24a, and 4.26a

To a solution of Grubbs second-generation metathesis catalyst (0.142 g, 0.17 mmol, 1 mol%) in anhydrous dichloromethane (100 mL) was added a solution containing 2-allyl-2-methylcyclohexane-1,3-dione[11] (2.77 g, 16.7 mmol, 100 mol%) in dichloromethane (70 mL) and acrolein (2.2 mL, 33.4 mmol, 200 mol%). The solution was refluxed overnight under an argon atmosphere. After removal of the solvent in *vacuo* the dark brown residue was purified *via* column chromatography (SiO_2: hexane/ethyl acetate, 4:1) to yield **4.18a** (1.77 g, 64%).

Representative Procedure for the Synthesis of Substrates 4.20a, and 4.21a

To a solution of 2-methyl-2-propionaldehyde-1,3-cyclopentanedione[5] (1.53 g, 9.08 mmol, 100 mol%) in 50 mL chloroform was added wittig reagent (formylmethylene)triphenylphosphorane (5.54 g 18.16 mmol, 200 mol%). The mixture was stirred overnight at 50 °C and then concentrated in *vacuo* to give a wet brown solid. This material was purified *via* column chromatography (SiO_2: hexane/ ethyl acetate, 9:1 to 7:3) to yield **4.20a** (0.632 g, 35%).

Procedure for the Synthesis of Substrates 4.23a

To a vigorously stirred mixture of 2-methyl-1, 3-indanedione[22] (1 g, 6.25 mmol, 100 mol%) and H_2O (15 mL) was added acrolein (0.6 mL, 9.37 mmol, 150 mol%). The mixture was stirred at room temperature for 15h and then extracted with dichloromethane (3 x 20 mL), dried over $MgSO_4$ and concentrated in *vacuo* to give a yellow oil (1.27 g 94% yield) of sufficient purity for the next step. This material (1 g, 4.63 mmol 100 mol%) was refluxed in chloroform with the wittig reagent (formylmethylene)triphenylphosphorane (2.82 g, 9.26 mmol, 200 mol%) for 18h. Product purification was done *via* column chromatography (SiO_2: hexane/ ethyl acetate, 8:2) to give a yellow oil (0.56 g, 40%).

(Benzylpropionylamino)-acetic acid ethyl ester

To a solution containing benzylamino-acetic acid ethyl ester[23] (13.5 g, 69.7 mmol, 100 mol%) in chloroform (100 mL) and triethylamine (20 mL, 139.8 mmol, 200 mol%) at 0 ºC, was added propionyl chloride (7.2 mL, 76.8 mmol, 110 mol%) dropwise over 1h. The mixture was stirred for an additional hour at room temperature and then diluted with chloroform 200 mL and washed with 5% aqueous acetic acid (1 X 100 mL), water (1 X 200 mL), brine (1 X 100 mL), and dried over $MgSO_4$. The organic layer was evaporated in *vacuo* to afford a yellow liquid (17.24g, 99%) of sufficient purity for the next step.

3- Allyl-1-benzyl-3-methylpyrrolidine-2,4-dione

To a refluxing suspension of NaH (60% dispersion in mineral oil) (1.0 g, 22.07 mmol, 110 mol%) in THF (50 mL), was added dropwise a solution of

(benzylpropionylamino)-acetic acid ethyl ester (5.0 g, 20.07 mmol, 100 mol%), in THF (50 mL). After addition was complete the reaction was refluxed for 12h during which a pale yellow solid formed. The mixture was cooled and the solid was filtered and dried in *vacuo* to yield a pale yellow solid (5.04g, 99%), of sufficient purity for the next step. To this material (3.0 g, 11.06 mmol, 100 mol%) in water (11 mL) allylbromide (2.68 g, 22.12 mmol, 200 mol%) was added, this mixture was stirred at 50 °C for 15h. The reaction mixture was extracted with dichloromethane (3 X 10 mL), dried over $MgSO_4$ and concentrated in *vacuo* to give a yellow oil. This material was purified *via* column chromatography (SiO_2: hexane/ethyl acetate, 8:2 to 6:4) to yield 1.72g, 64% of the title compound

Benzoic acid 2-oxo-hex-5-enyl ester

Benzoyl chloride (1.45 mL, 12.5 mmol, 110 mol%), was added dropwise to a stirred solution of 1-hydroxy-hex-5-en-2-one [24] (1.30 g, 11.3 mmol, 100 mol%) in pyridine (20 mL) and di-isopropylethylamine (1 mL) at 0 °C. The solution was stirred at this temperature for 1h and then at room temperature for 2h. The reaction mixture was evaporated at reduced pressure, the residue was treated with 20 mL of ice cold saturated with $NaHCO_3$ and extracted with ethyl acetate (2 X 100 mL). The organic phase was washed with 6M HCl (1 X 10 mL), aqueous $NaHCO_3$ (1 X 10 mL), and water (1 X 5 mL). The solution was dried over $MgSO_4$ and the solvent removed in *vacuo* to afford a pale yellow liquid. This product was purified *via* column chromatography (SiO_2: hexane/ethyl acetate, 4:1) to yield (2.43g, 99%) of a colorless liquid.

Representative Procedure for Catalytic Aldol Cycloreduction of Keto-enals 4.18a-4.26a

To a clean dry 25 mL round bottom flask charged with $Rh(COD)_2OTf$ (24 mg, 0.0515 mmol, 10 mol%) and triphenylphosphine (32 mg, 0.123 mmol, 24 mol%) was added 10 mL of dry THF. The mixture was stirred for 10 minutes under argon atmosphere, at which point **4.18a** (100 mg, 0.515 mmol, 100 mol%) and potassium carbonate (72 mg, 0.515 mmol, 100 mol%) was added. The system was purged with hydrogen gas and the reaction was allowed to stir at 40 ºC under 1 atm of hydrogen until complete consumption of substrate, at which point the solvent was evaporated and the product was purified *via* column chromatography

7a-Hydroxy-3a-methyl-4-oxo-octahydroindene-1-carboxylic acid 4.18b-acid derivative.

A chromic acid solution was added dropwise to a stirred solution of **4.18b** (0.050 g, 0.25 mmol, 100 mol%) in 2 mL ether at 0 °C. The addition continued until a persistent orange color was observed. The mixture was stirred for 30 minutes, at which point methanol was added until excess chromic acid had been destroyed. The mixture was filtered and the filtrate extracted with dichloromethane (3x10 mL). The extracts were combined, dried over $MgSO_4$, concentrated *in vacuo* and purified *via* silica gel column chromatography dichloromethane/ethyl acetate 4:1 to yield **4.18b**-acid derivative (0.036g, 74%) as a white solid.

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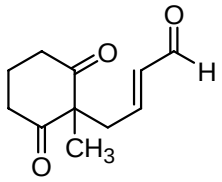
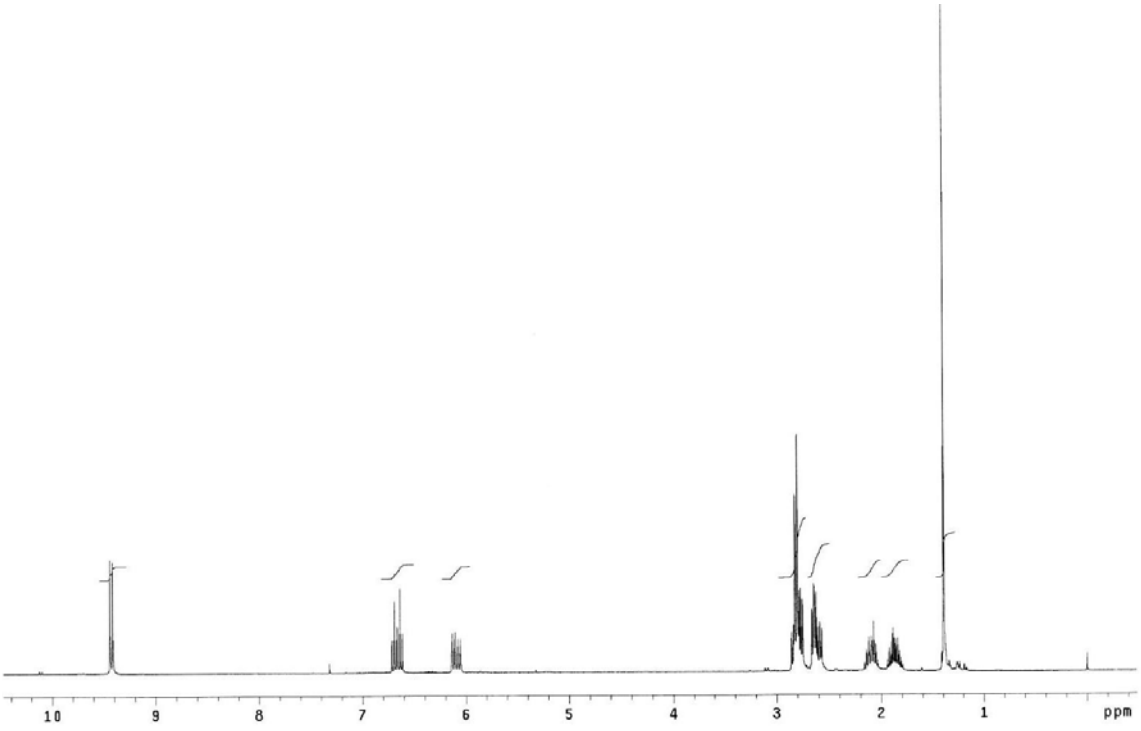
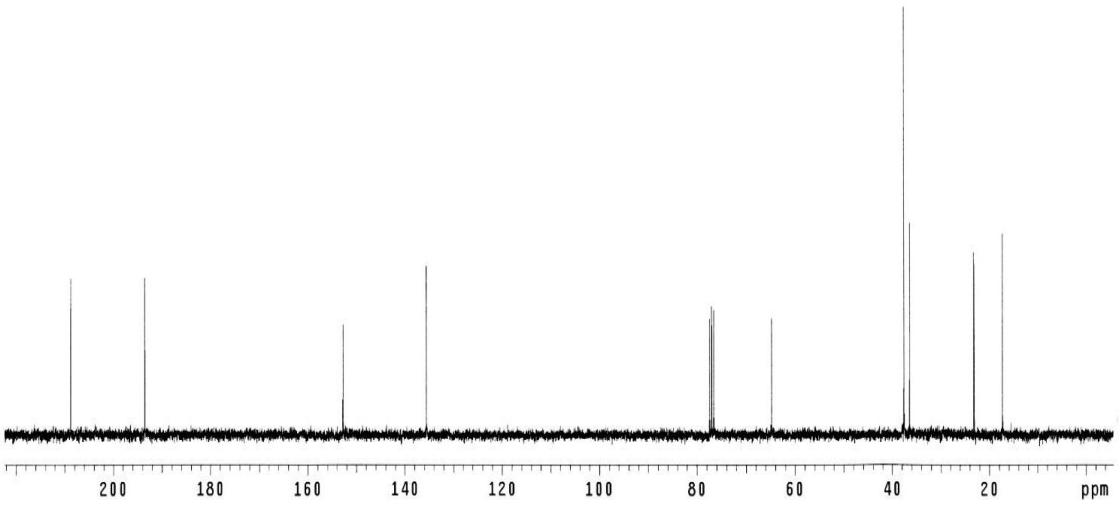
4.5 Spectroscopic Characterization Data



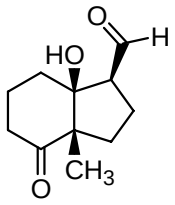
4-(1-Methyl-2,6-dioxocyclohexyl)but-2-enal 4.18a. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.43 (d, *J* = 7.9 Hz, 1H), 6.67 (dt, *J* = 15.6, 7.4 Hz, 1H), 6.09 (ddt, *J* = 15.6, 7.2, 1.3, Hz, 1H), 2.74 (m, 4H), 2.60 (m, 2H), 2.09 (m, 1H), 1.87 (m, 1H), 1.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.8, 193.6, 152.5, 135.6, 64.5, 37.6, 36.4, 23.2, 17.3. FTIR (NaCl): 2970, 2888, 2822, 1695, 1454, 1419, 1116, 917, 717, 640 cm^{-1}. HRMS calcd for $C_{11}H_{15}O_3$ [M+1] 195.1021 found 195.1016.



^{1}H NMR of **4.18a**

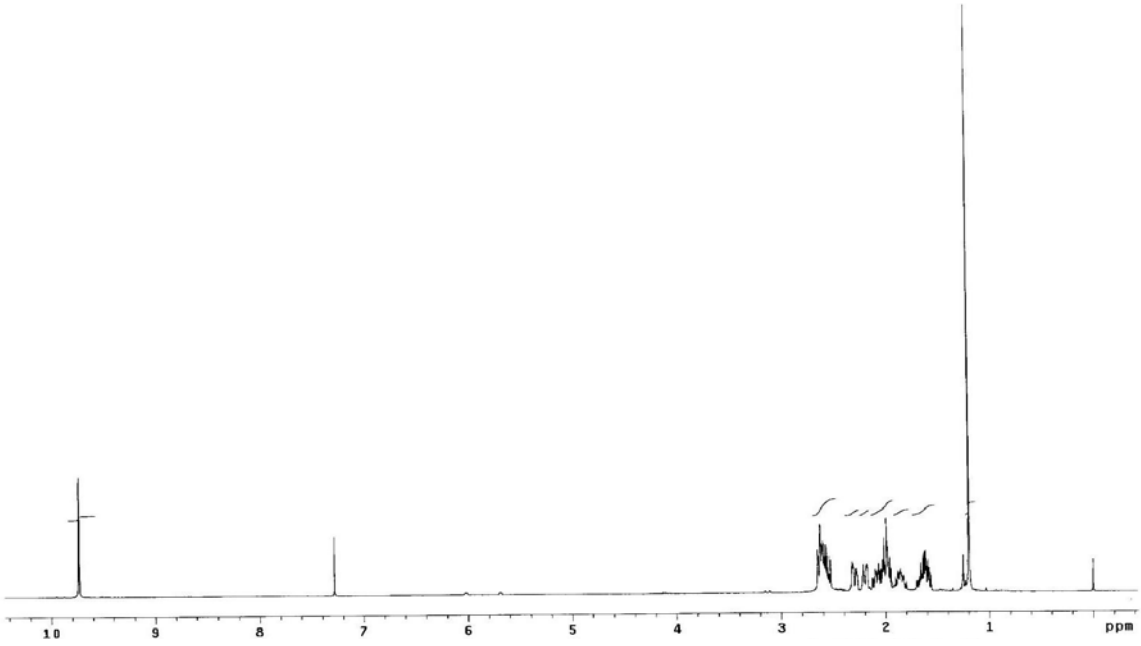


^{13}C NMR of **4.18a**

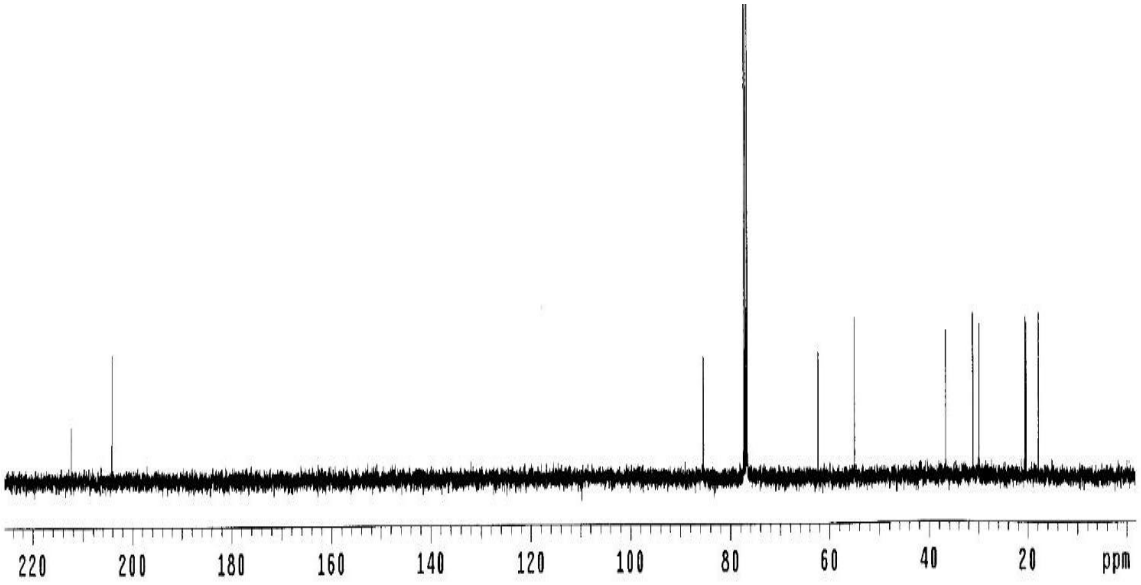


7a-Hydroxy-3a-methyl-4-oxo-octahydro-indene-1-carbaldehyde 4.18b

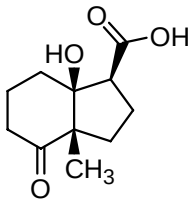
Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.74 (d, *J* = 1.7 Hz, 1H), 2.58 (m, 4H), 2.54 (m, 1H), 2.19 (m, 1H), 2.01 (m, 3H), 1.86 (m, 1H), 3.26 (m, 2H), 1.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.3, 204.1, 85.4, 62.3, 54.9, 36.7, 31.2, 29.9, 20.5, 20.3, 17.9. FTIR (NaCl): 3447, 2965, 2883, 1695, 1460, 1419, 1352, 1306, 1202, 1152, 1081, 989 cm^{-1}. HRMS: calcd for $C_{11}H_{15}O_3$ [M-1] 195.1021; found 195.1014.



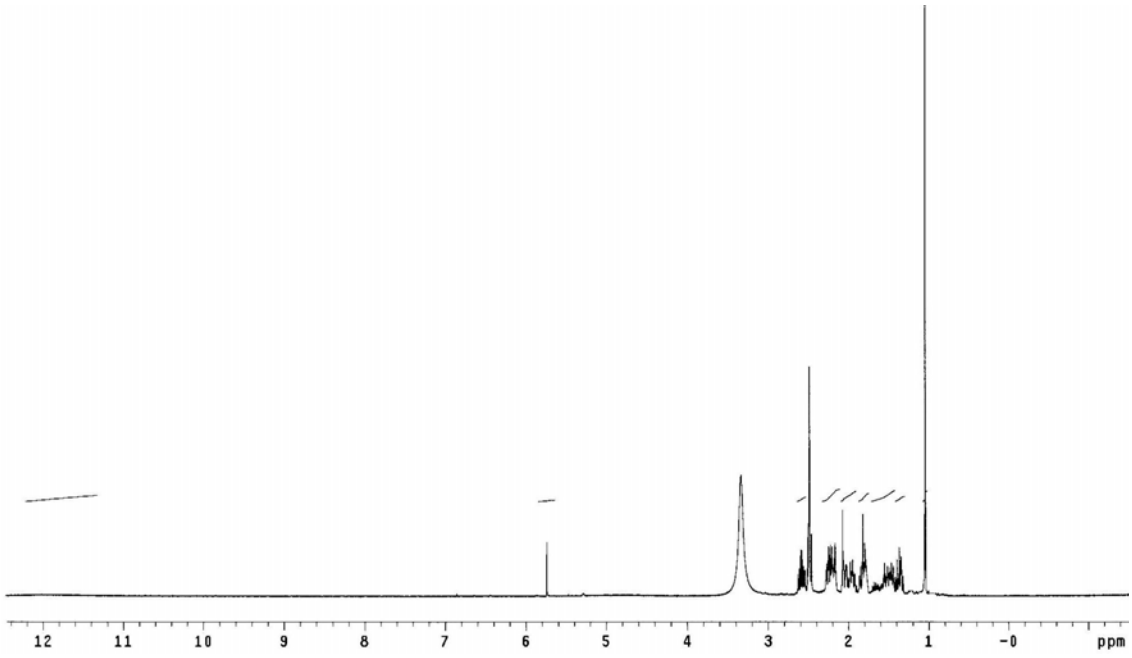
^{1}H NMR of **4.18b**



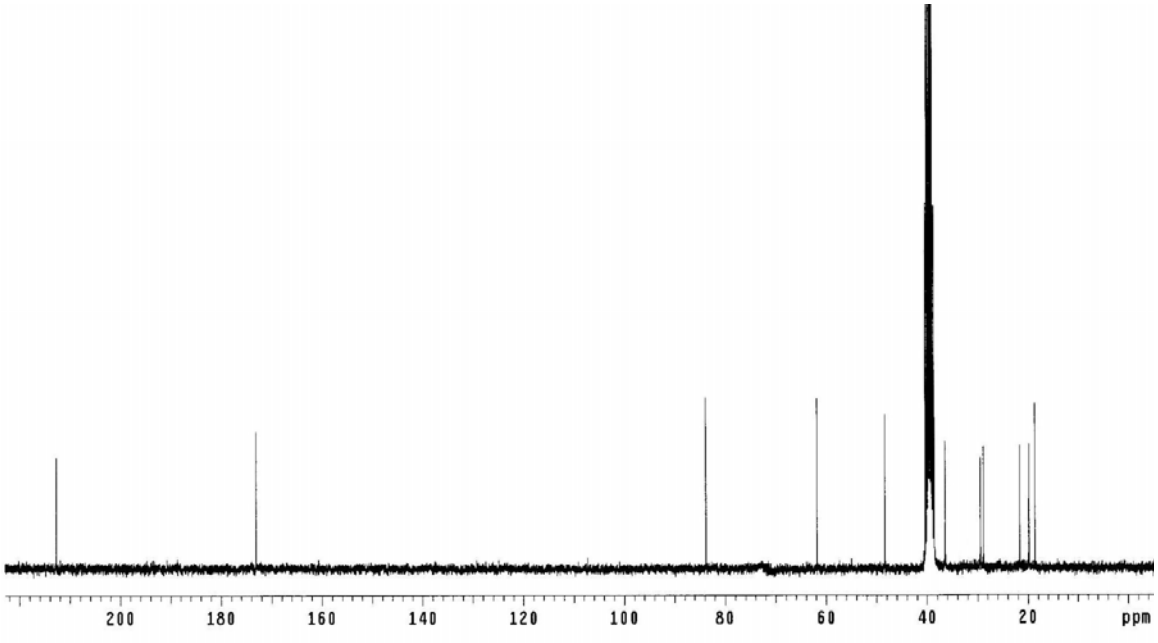
^{13}C NMR of **4.18b**



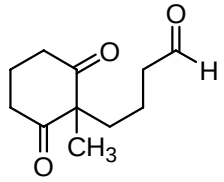
7a-Hydroxy-3a-methyl-4-oxo-octahydroindene-1-carboxylic acid 4.18b-acid derivative. ^{1}H NMR (400 MHz, dmso-d_6): δ 11.90 (br s, 1H), 5.74 (s, 1H), 2.58 (m, 1H), 2.23 (m, 3H), 2.07-1.92 (m, 2H), 1.83 (m, 2H), 1.49 (m, 2H), 1.36 (m, 1H), 1.04 (s, 3H). ^{13}C NMR (75 MHz, dmso-d_6): δ 212.8, 173.1, 83.8, 61.8, 48.4, 36.4, 29.4, 28.8, 21.6, 19.8, 18.5. FTIR (NaCl): 3462, 2950, 2683, 1705, 1460, 1430, 1210, 1080, 930 cm^{-1}. HRMS: calcd for $C_{11}H_{17}O_4$ [M+1] 213.1127; found 213.1130. MP 118-120 °C.



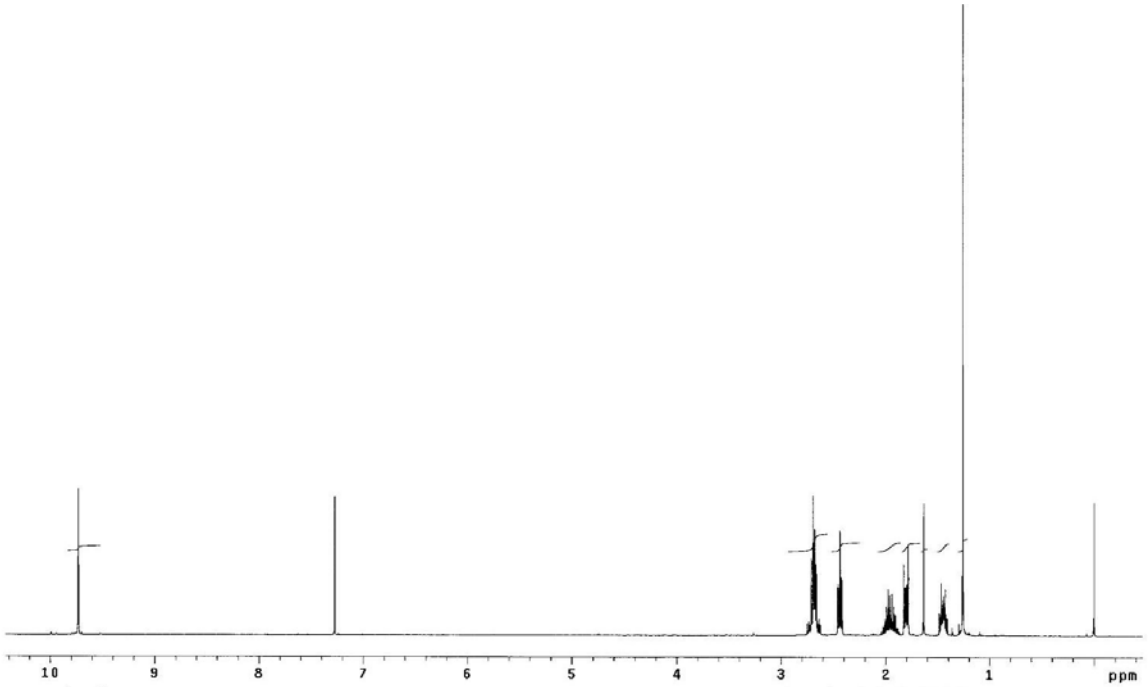
^{1}H NMR of **4.18b**-acid derivative



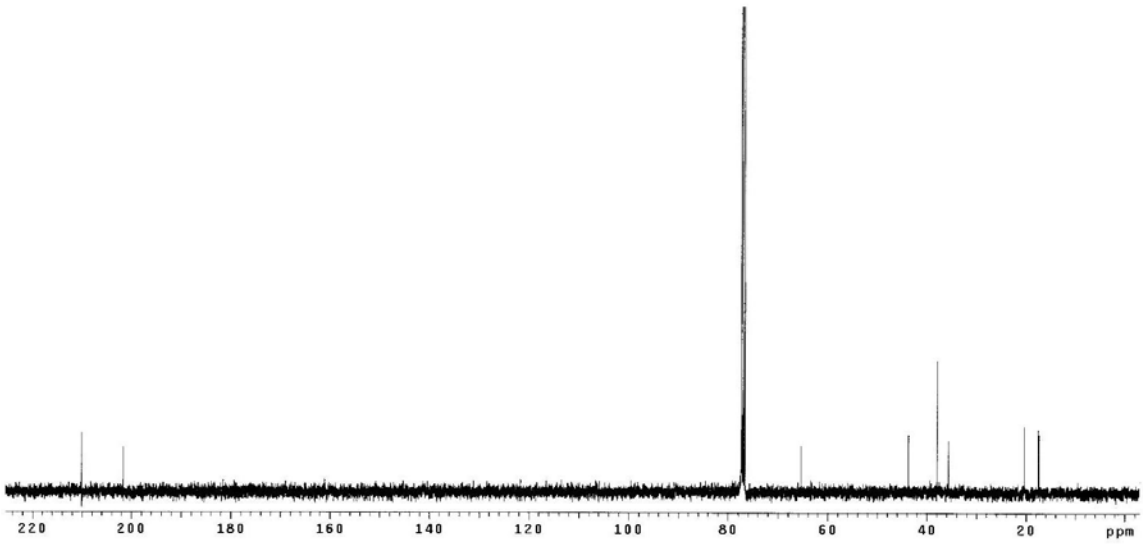
^{13}C NMR of **4.18b**-acid derivative



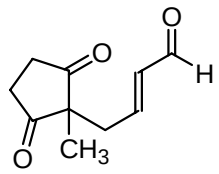
4-(1-Methyl-2,6-dioxocyclohexyl)butyraldehyde 4.18c. Yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (t, *J* = 1.3 Hz, 1H), 268 (m, 4H), 2.43 (td, *J* = 5.8, 1.3 Hz, 2H), 2.00 (m, 2H), 1.80 (m, 2H), 1.45 (m, 2H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.1, 201.6, 65.4, 43.7, 37.9, 35.6, 20.4, 17.6, 17.4. FTIR (NaCl): 2964, 2871, 1727, 1688, 1454, 1427, 1334, 1131, 933, 839 cm^{-1}. HRMS: calcd for $C_{11}H_{17}O_3$ [M+1] 197.1178; found 197.1185.



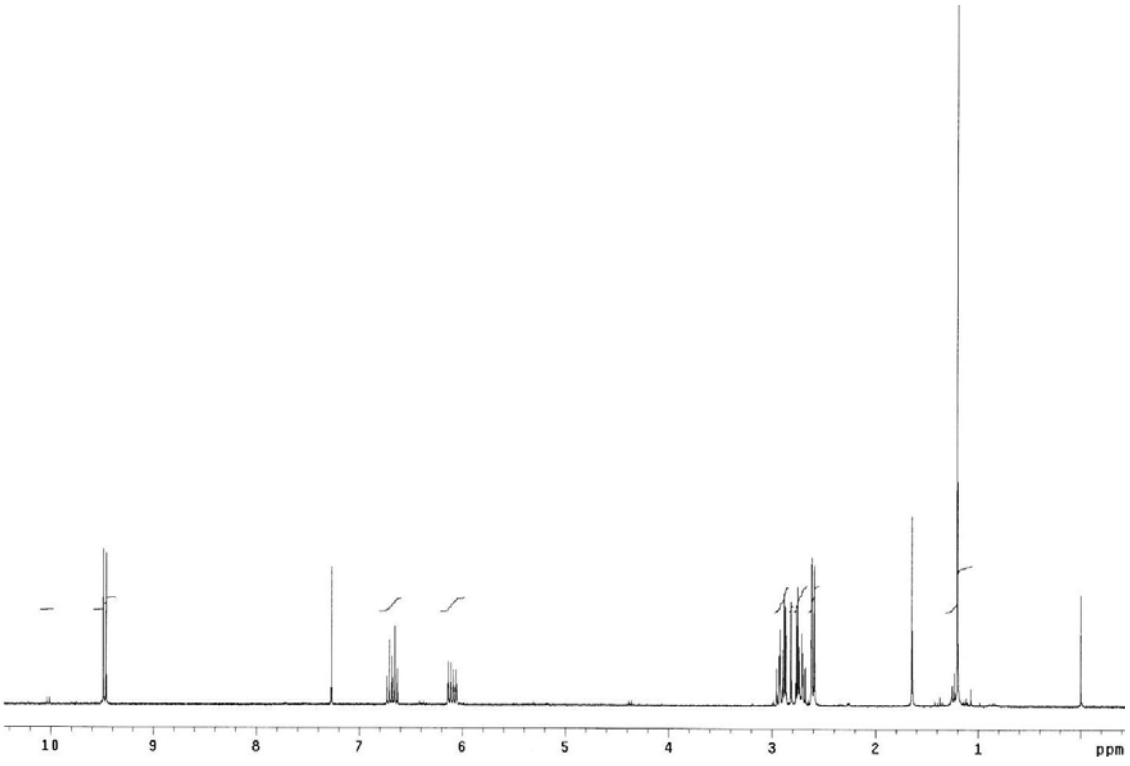
^{1}H NMR of **4.18c**



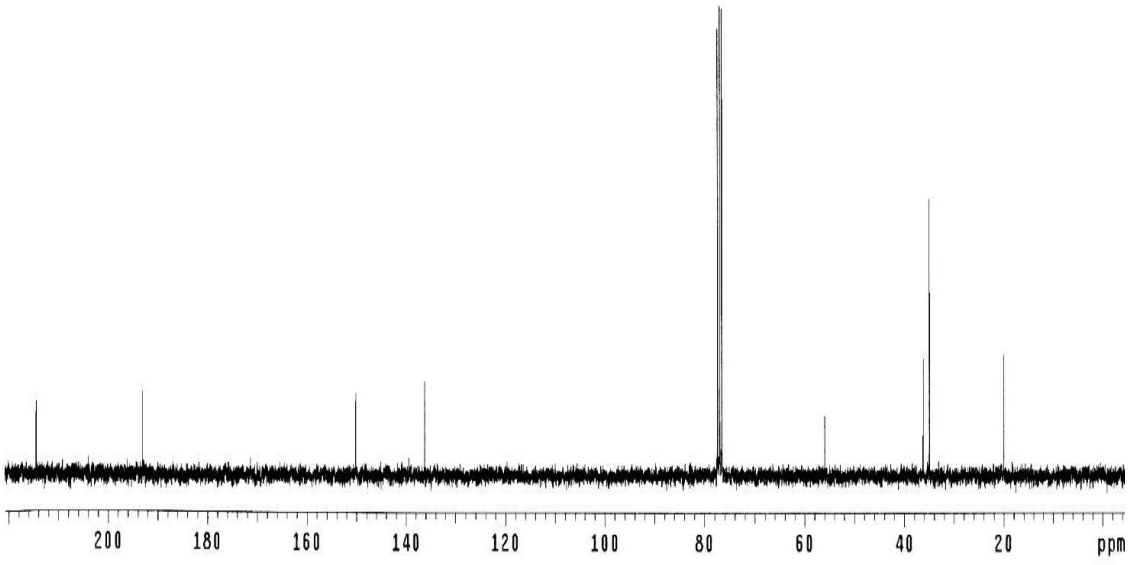
^{13}C NMR of **4.18c**



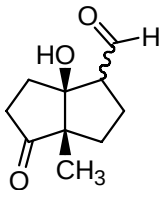
4-(1-Methyl-2,5-dioxocyclopentyl)but-2-enal 4.19a. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.48 (d, *J* = 7.7 Hz, 1H), 6.71 (dt, *J* = 15.6, 7.4 Hz, 1H), 6.09 (ddt, *J* = 15.6, 7.9, 1.3 Hz, 1H), 2.91 (m, 2H), 2.73 (m, 2H), 2.61 (dd, *J* = 8.7, 1.3 Hz, 2H), 1.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.5, 193.1, 150.1, 136.2, 55.9, 36.2, 34.9, 20.0. FTIR (NaCl): 2965, 2842, 2755, 1736, 1680, 1342, 1413, 1127, 978, 814 cm^{-1}.HRMS: calcd for $C_{10}H_{13}O_3$ [M+1] 181.0865 found 181.0864.



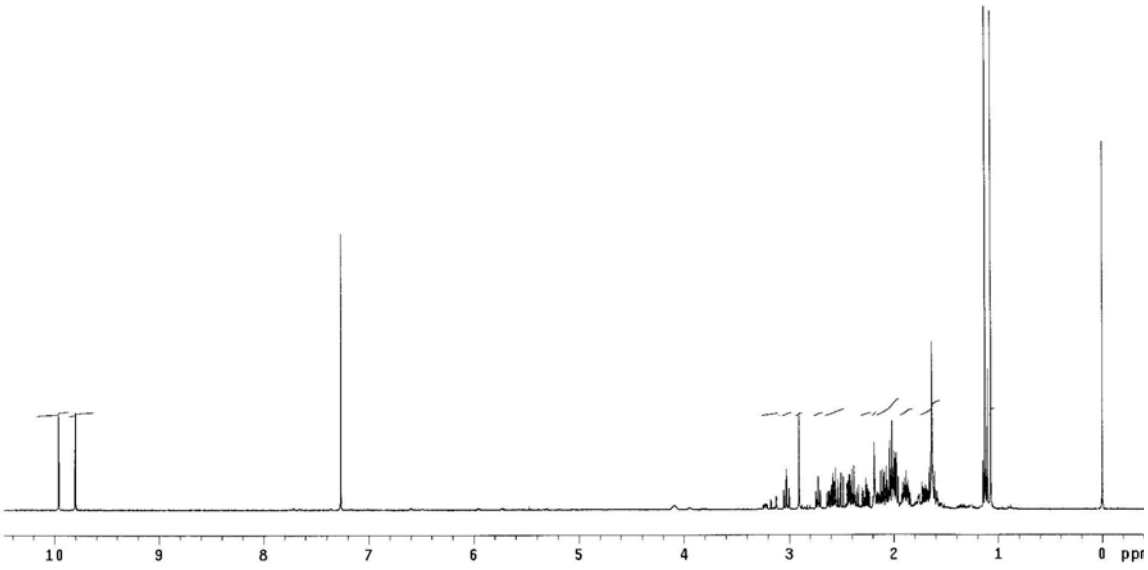
^{1}H NMR of **4.19a**



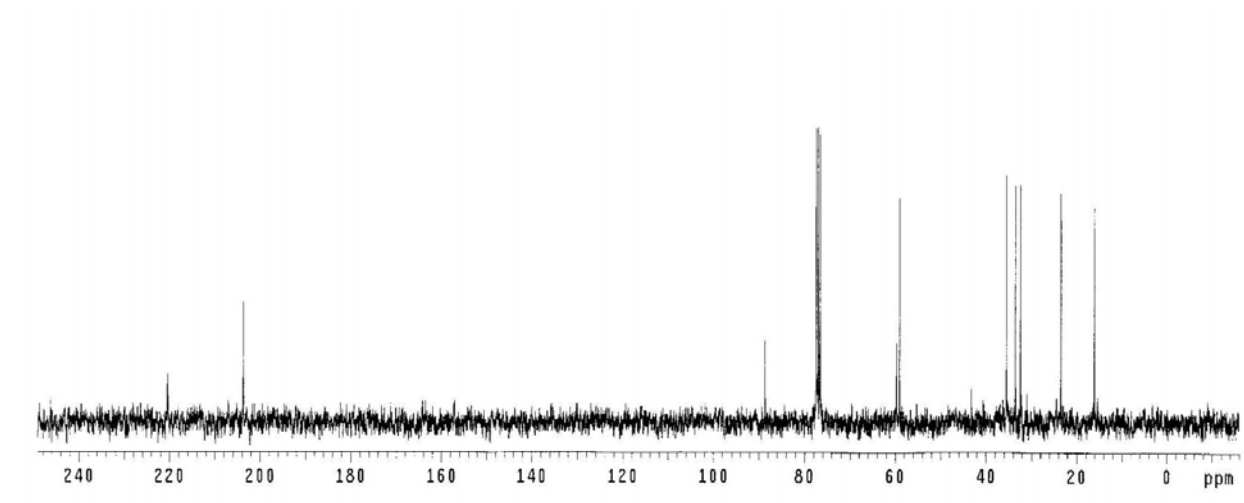
^{13}C NMR of **4.19a**



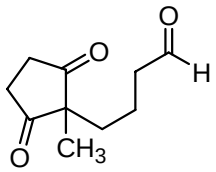
6a-Hydroxy-3a-methyl-4-oxo-octahydropentalene-1-carbaldehyde 4.19b. This product was obtained as an inseparable mixture of syn/anti (2:1) diastereomers. Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.76 (d, *J* =1.2 Hz, 0.5H (anti)), 9.80 (d, *J* = 1.5 Hz, 1H (syn), 3.00 (td, *J* = 9.6, 1.4 Hz, 1H), 2.92 (s, 1H), 2.70 (td, *J* = 8.5, 1.4, Hz, 1H), 2.58 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.4, 203.6, 88.6, 59.7, 59.0, 35.5, 33.5, 32.3, 23.8, 16.9. FTIR (NaCl): 3428, 2965, 2875, 1719, 1641, 1556, 1458, 1256, 1073, 754 cm^{-1}. HRMS: calcd for $C_{10}H_{15}O_3$ [M+1] 183.1021; found 183.1025.



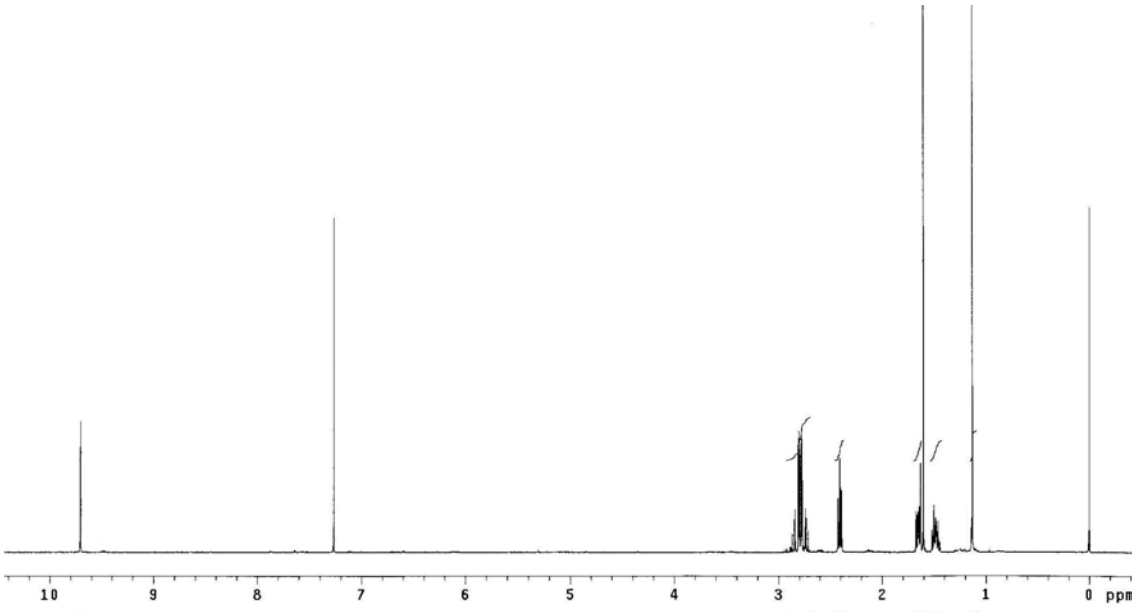
^{13}H NMR of **4.19b**



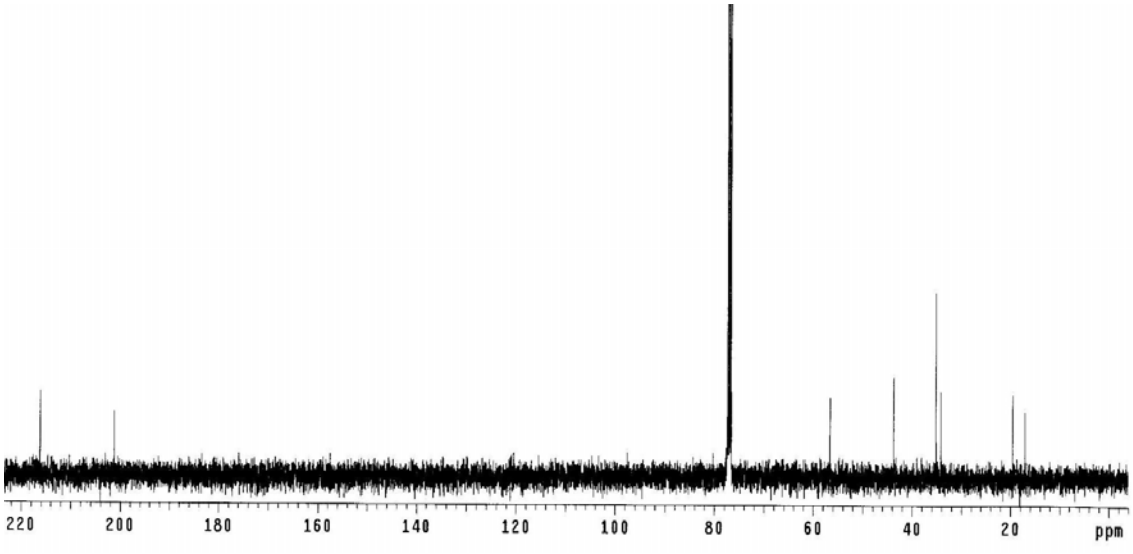
^{13}C NMR of **4.19b**



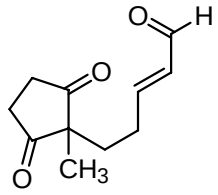
4-(1-Methyl-2,5-dioxocyclopentyl)butyraldehyde 4.19c.Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (t, *J* = 1.4 Hz, 1H), 2.81 (m, 4H), 2.41 (td, *J* = 7.2, 1.4 Hz, 2H), 1.65 (m, 2H), 1.53 (m, 2H), 1.13 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 216, 201.2, 56.6, 43.7, 35.1, 34.2, 19.6, 17.1. FTIR (NaCl): 2936, 2869, 1724, 1452, 1378, 1269, 1161, 1109, 1048, 986 cm^{-1}. HRMS: calcd for $C_{10}H_{15}O_3$ [M+1] 183.1021; found 183.1015.



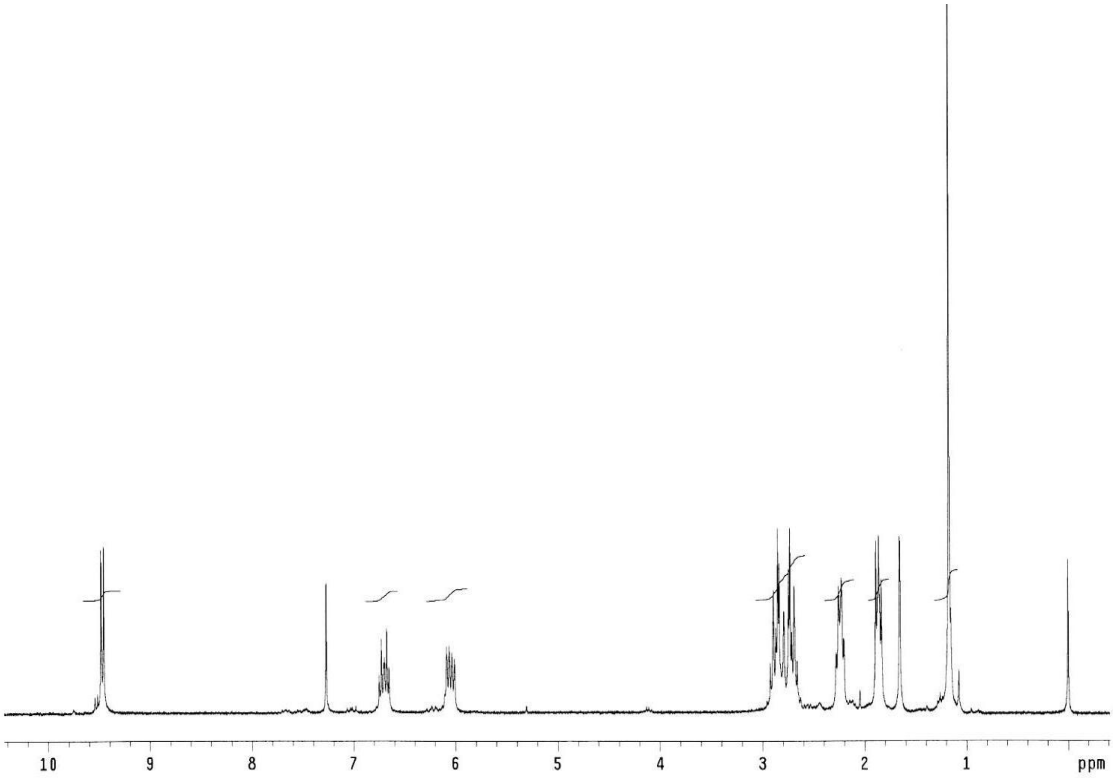
^{13}H NMR of **4.19c**



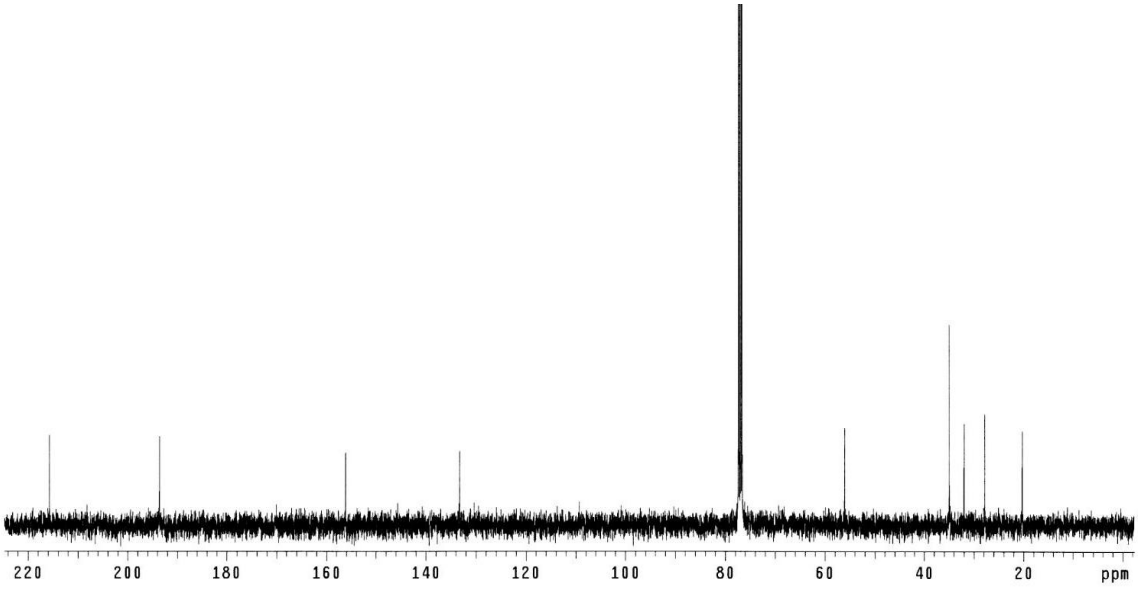
^{13}C NMR of **4.19c**



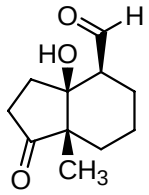
5-(1-Methyl-2,5-dioxocyclopentenyl)pent-2-enal 4.20a. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.47 (d, *J* = 8.6 Hz, 1H), 6.69 (dt, *J* = 15.6, 6.7 Hz, 1H), 6.05 (dd, *J* = 15.6, 7.9 Hz, 1H), 2.79 (m, 4H), 2.23 (m, 2H), 1.86 (t, *J* = 7.9 Hz, 2H), 1.17 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 215.7, 193.6, 156.2, 133.3, 56.0, 35.0, 32.0, 27.8, 20.3. FTIR (NaCl): 2930, 2847, 1721, 1680, 1634, 1450, 1413, 1291, 1127, 1081, 994 cm^{-1}. HRMS: calcd for $C_{11}H_{15}O_3$ [M+1] 195.1012 found 195.1014



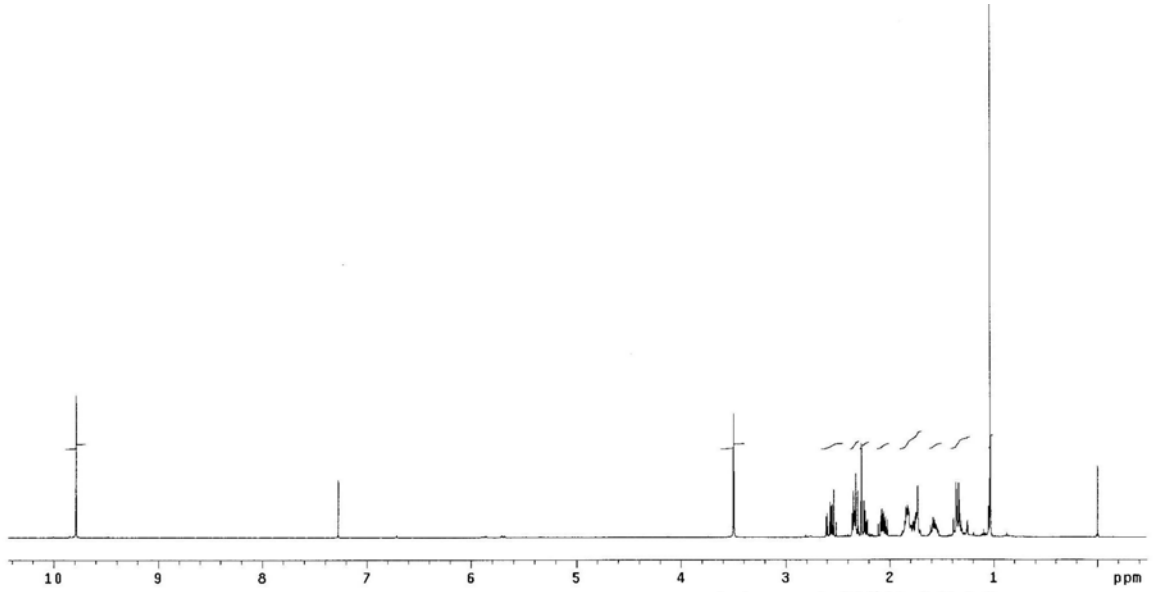
^{1}H NMR of **4.20a**



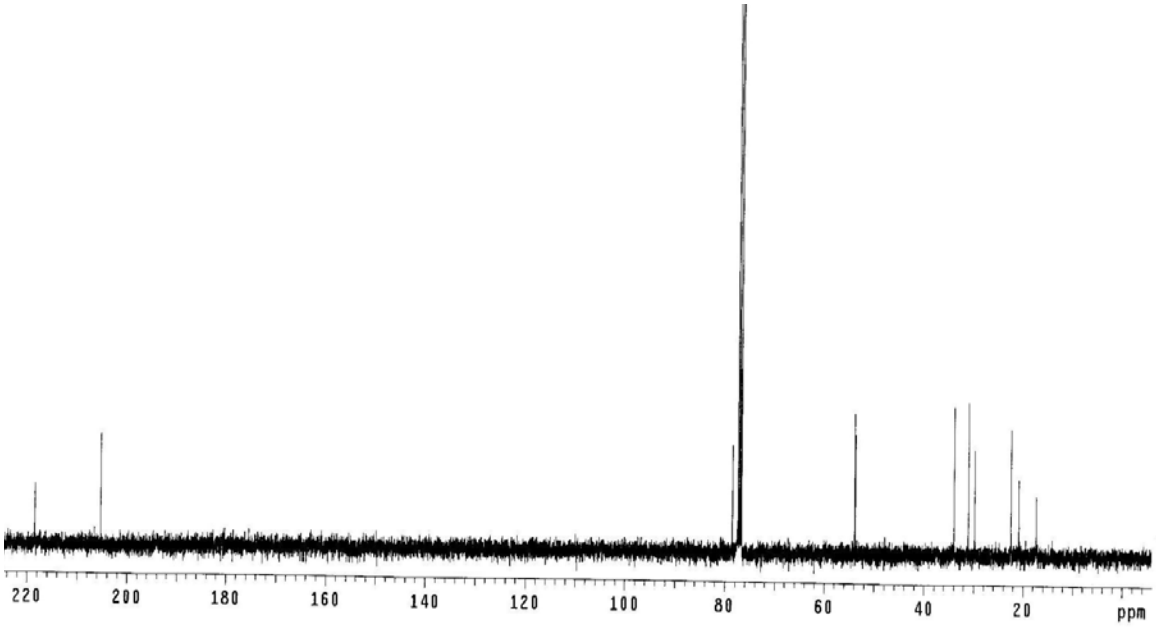
^{13}C NMR of **4.20a**



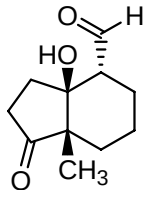
3a-Hydroxy-7a-methyl-1-oxo-octahydroindene-4-carbaldehyde 4.20b-*syn*. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (d, *J* = 0.7 Hz, 1H), 3.50 (s, 1H), 2.55 (m, 1H), 2.33 (m, 1H), 2.24 (m, 2H), 2.06 (m, 1H), 1.78 (m, 3H), 1.57 (m, 1H), 1.34 (m, 2H), 1.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.5, 205.3, 78.5, 53.9, 53.8, 33.9, 31.1, 29.8, 22.4, 20.8, 17.4. FTIR (NaCl): 3416, 2939, 2848, 1711, 1716, 1454, 1378, 1301, 118, 1071, 1014 cm^{-1}. HRMS: calcd for $C_{11}H_{17}O_3$ [M+1] 197.1178; found 197.1181.



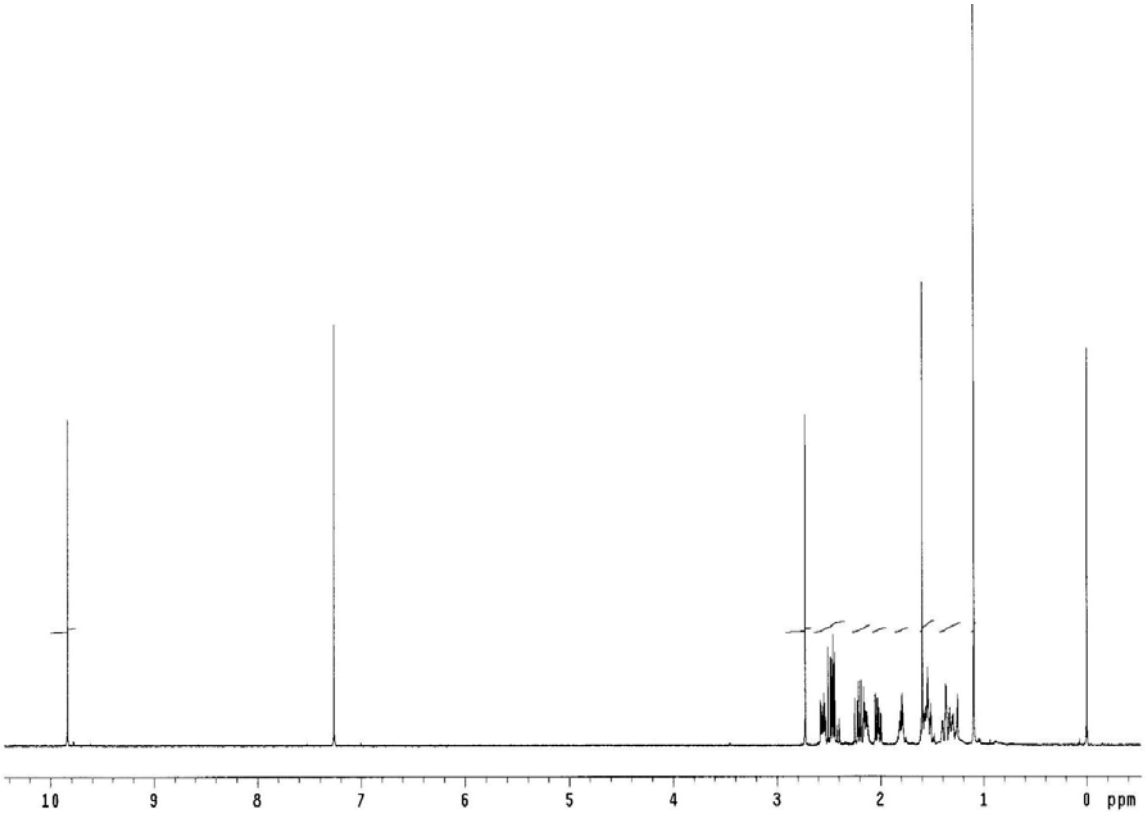
^{1}H NMR of **4.20b-*syn***



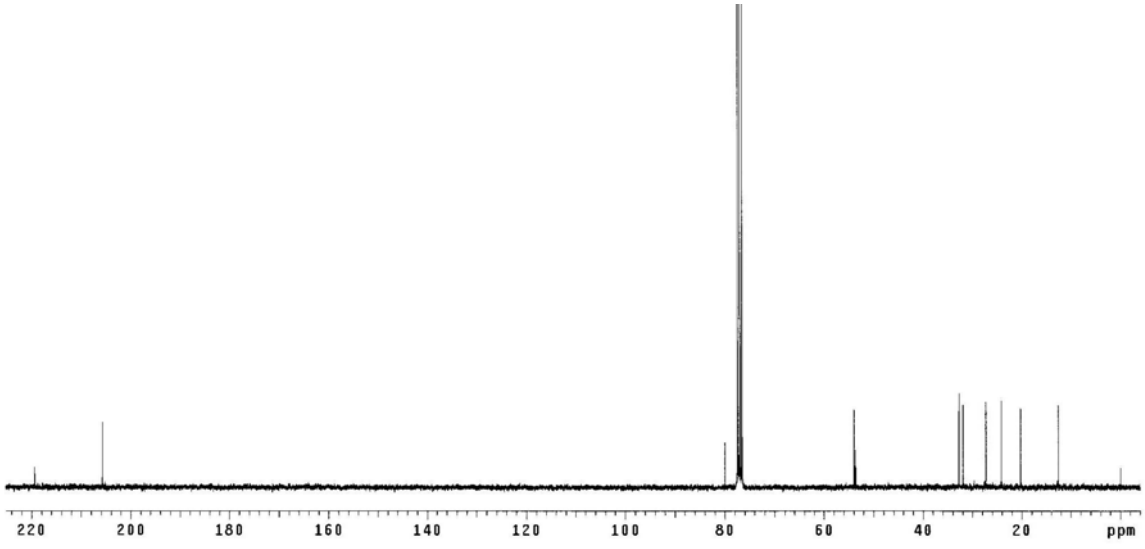
^{13}C NMR of **4.20b-*syn***



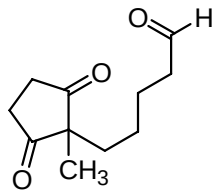
3a-Hydroxy-7a-methyl-1-oxo-octahydroindene-4-carbaldehyde 4.20b-*anti*. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): 9.84 (d, J = 0.7 Hz, 1H), 2.72 (s, 1H), 2.55 (m, 2H), 2.47 (m, 2H), 2.22 (m, 1H), 1.80 (m, 1H), 1.55 (m, 2H), 1.35 (m, 3H), 1.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 219.4, 205.7, 78.0, 53.9, 53.6, 32.7, 31.9, 27.3, 24.1, 20.2, 12.6. FTIR (NaCl): 3421, 2934, 2840, 1710, 1644, 1449, 1306, 1219, 1178, 1086, 1060, 947 cm^{-1}. HRMS: calcd for $C_{11}H_{17}O_3$ [M+1] 197.1178 found 197.1181.



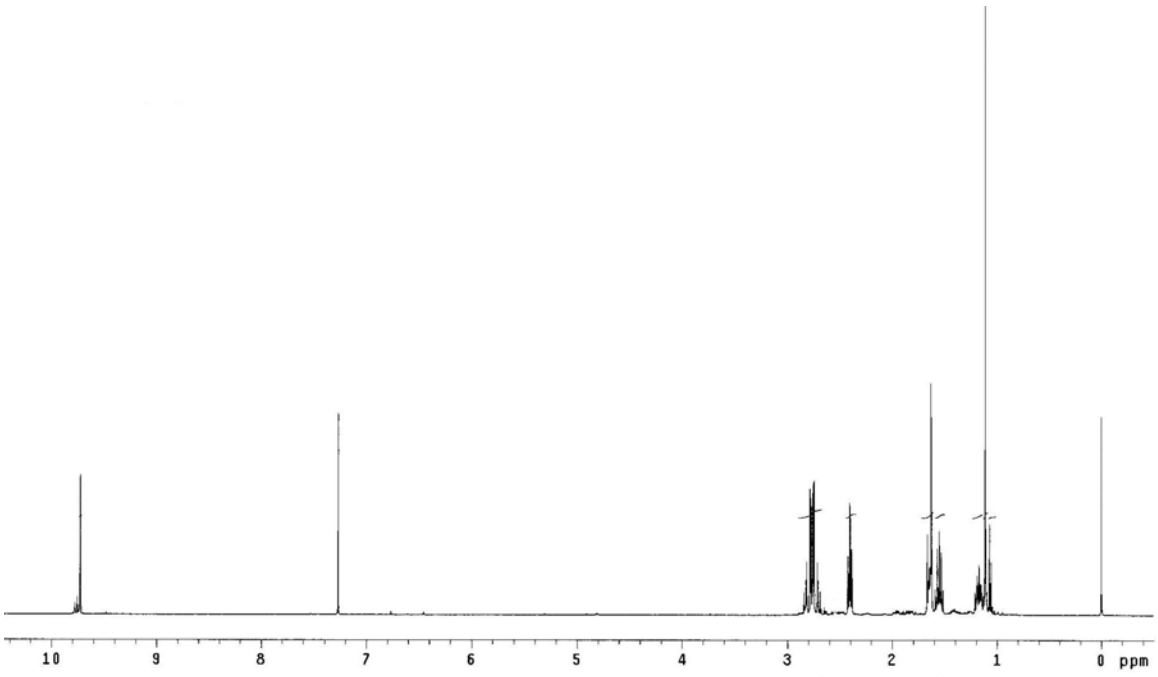
^{1}H NMR of **4.20b-*anti***



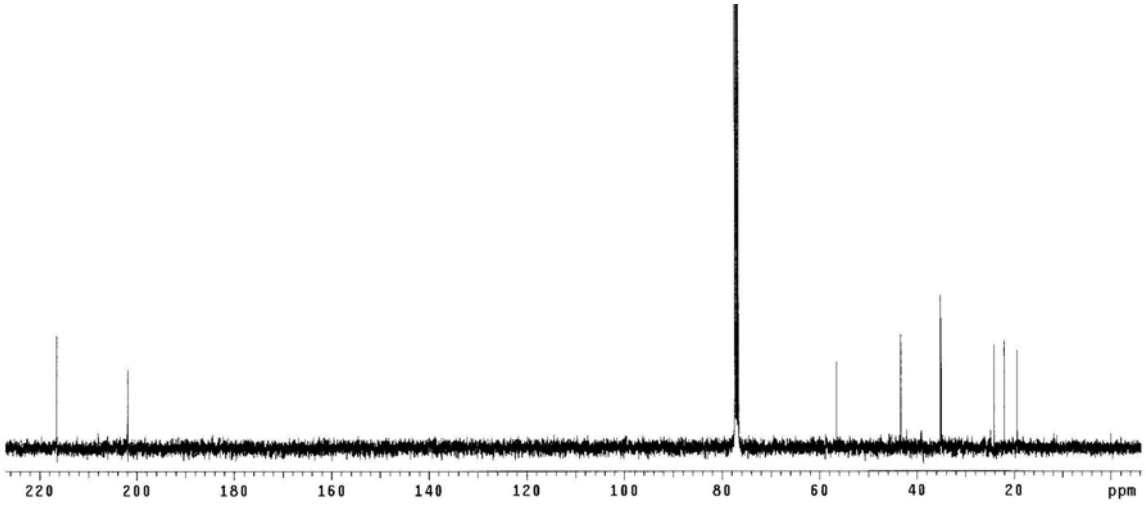
^{13}C NMR of **4.20b-*anti***



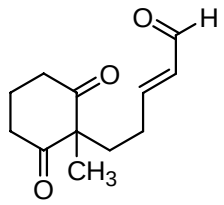
5-(1-Methyl-2,5-dioxo-cyclopentyl)pentanal 4.20c. Yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (t, *J* = 1.5 Hz 1H), 2.76 (m, 4H), 2.41 (td, *J* = 7.2, 1.5 Hz, 2H), 1.64 (m, 2H), 1.55 (q, *J* = 7.5 Hz, 2H), 1.15 (m, 2H), 1.11 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 216.5, 201.9, 56.5, 43.3, 35.2, 35.0, 24.1, 22.1, 19.4. FTIR (NaCl): 2929, 2719, 1762, 1716, 1460, 1419, 1373, 1291, 1096, 1045, 989 cm^{-1}. HRMS: calcd for $C_{11}H_{17}O_3$ [M+1] 197.1178; found 197.1181.



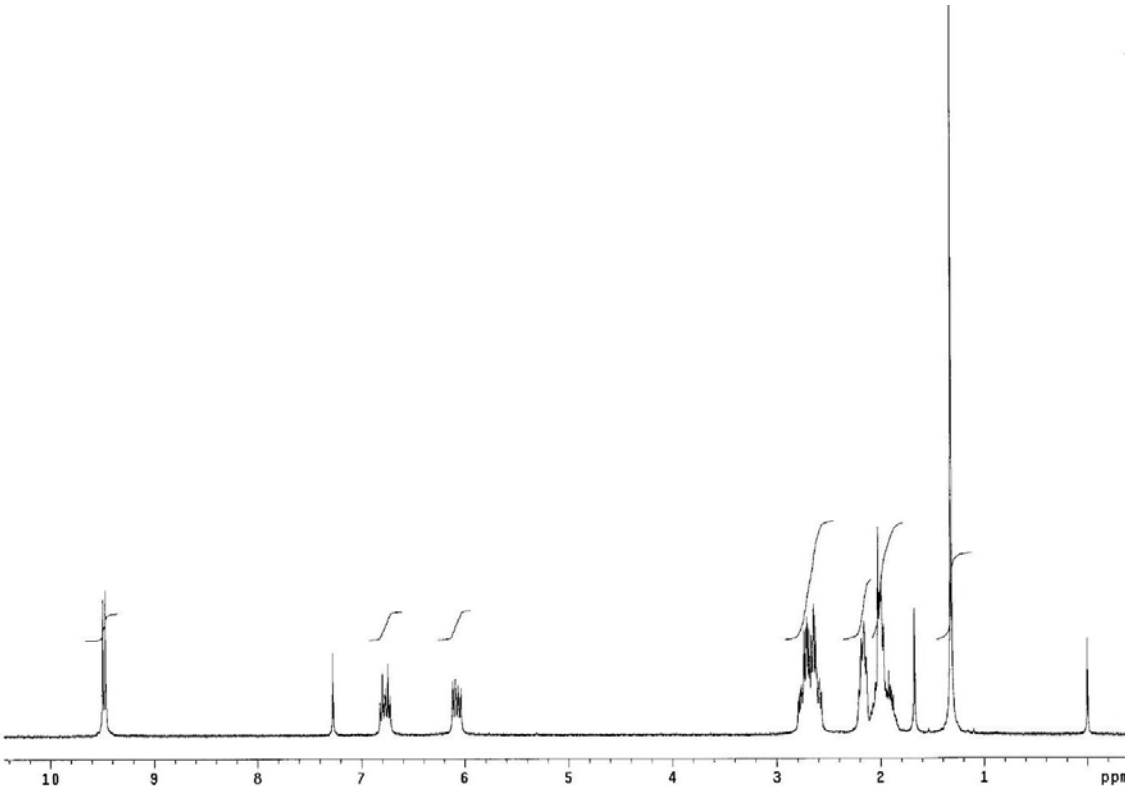
^{1}H NMR of **4.20c**



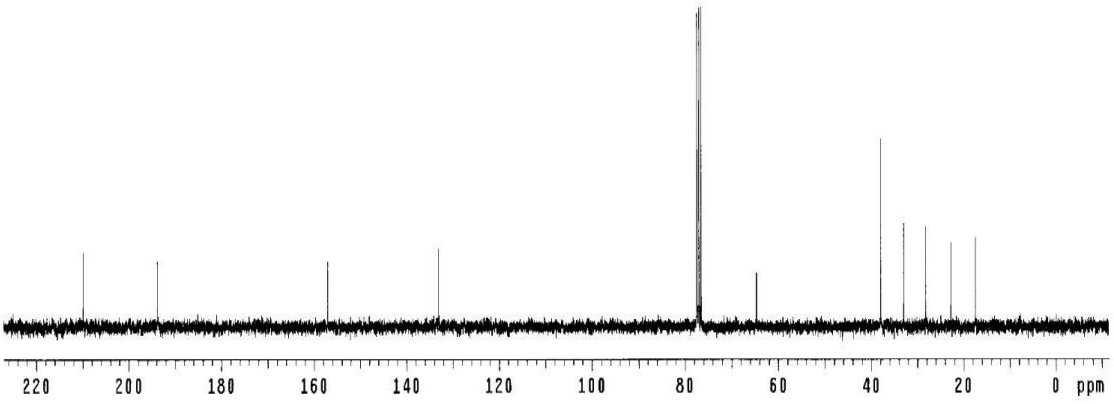
^{13}C NMR of **4.20c**



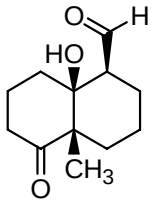
5-(1-Methyl-2,6-dioxocyclohexyl)pent-2-enal 4.21a. Yellow solid ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.48 (d, *J* = 7.9 Hz, 1H), 6.77 (dt, *J* = 15.6, 6.7 Hz, 1H), 6.08 (dd, 15.6, 7.9 Hz, 1H), 2.71 (m, 4H), 2.04 (m, 2H), 1.99 (m, 4H), 1.32 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$): δ 209.9, 193.9, 157.1, 133.0, 64.6, 38.0, 32.9, 28.2, 22.7, 17.4. FTIR (NaCl): 2990, 2951, 2834, 1724, 1693, 1642, 1456, 1219, 1130, 1025, 916 cm^{-1}. HRMS: calcd for $C_{12}H_{17}O_3$ [M+1] 209.1178 found 209.1175. MP 51-53 °C.



^{1}H NMR of **4.21a**

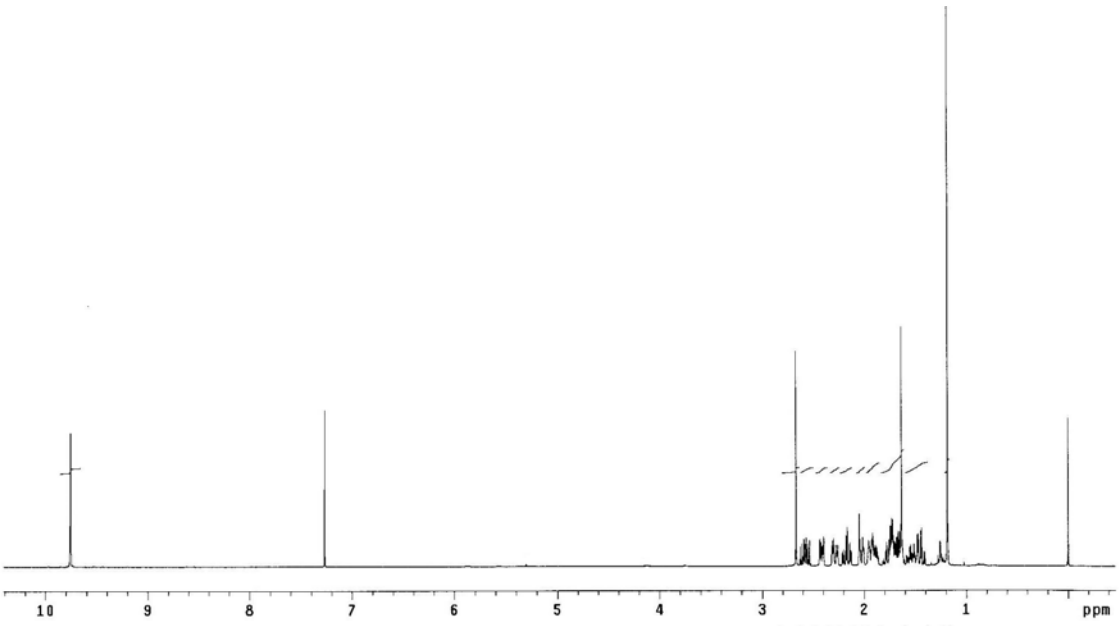


^{13}C NMR of **4.21a**

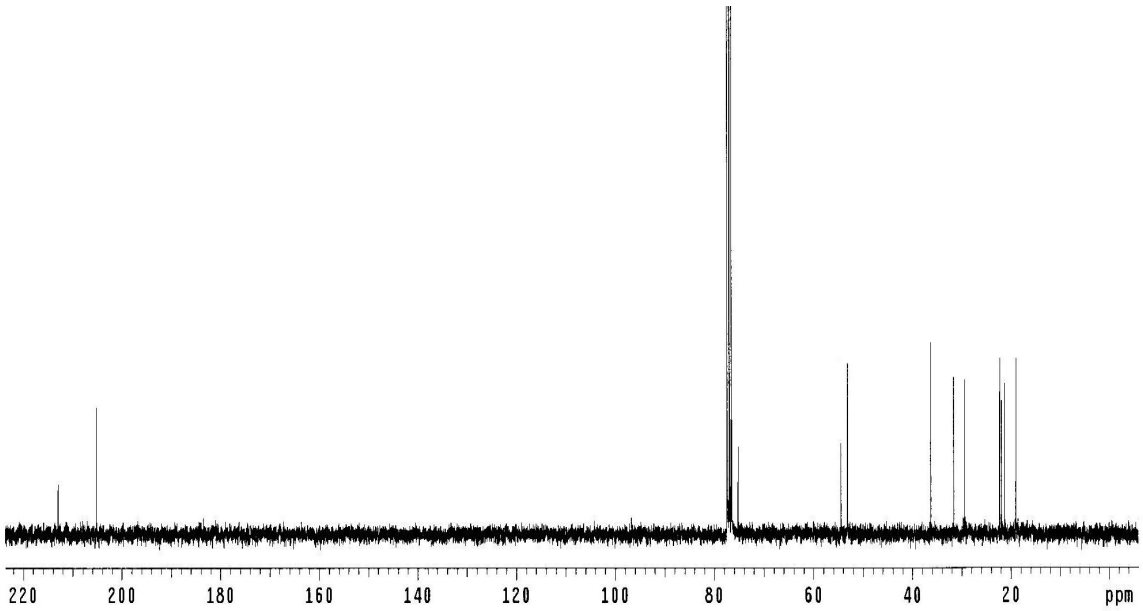


8a-Hydroxy-4a-methyl-5-oxodecahydronaphthalene-1-carbaldehyde 4.21b.

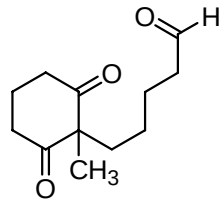
White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.76 (d, *J* = 2.7 Hz, 1H), 2.67 (s, 1H), 2.58 (m, 1H), 2.41 (m, 1H), 2.28 (m, 1H), 2.17 (m, 1H), 2.02 (m, 1H), 1.91 (m, 2H), 1.71 (m, 4H), 1.49 (m, 2H), 1.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.9, 205.2, 75.2, 54.4, 53.2, 36.3, 31.6, 29.4, 22.3, 21.9, 21.3, 18.9. FTIR (NaCl): 3417, 2945, 2845, 1712, 1629, 1459, 1178, 1166, 962 cm^{-1} HRMS: calcd for $C_{12}H_{19}O_3$ 211.1334; [M+1] found 211.1330. MP 59-61 °C.



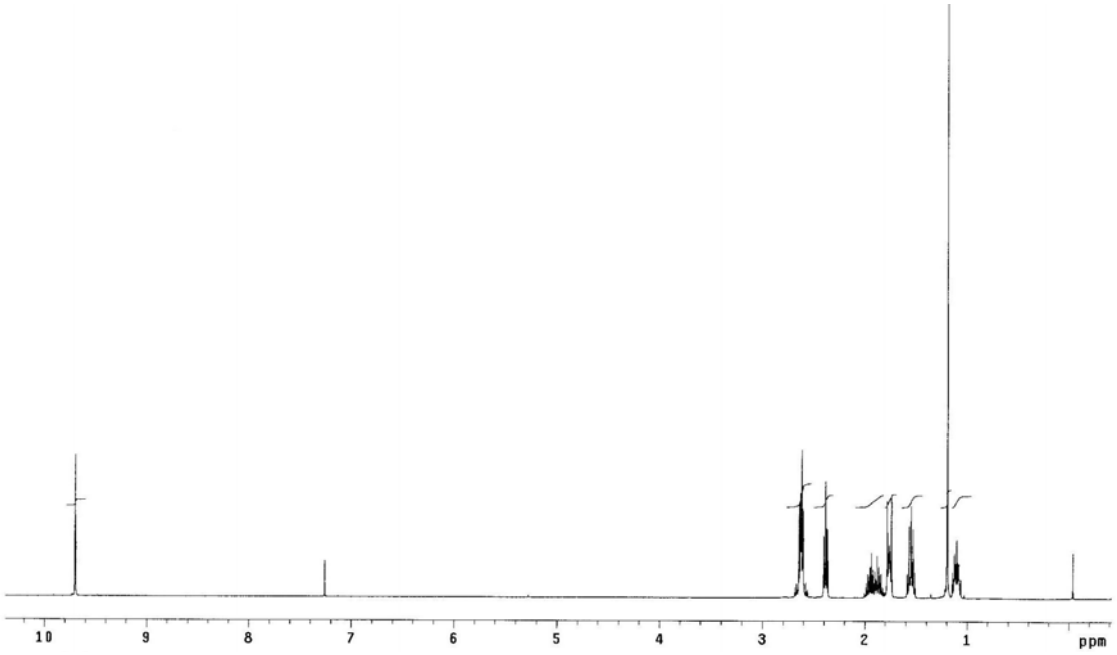
^{1}H NMR of **4.21b**



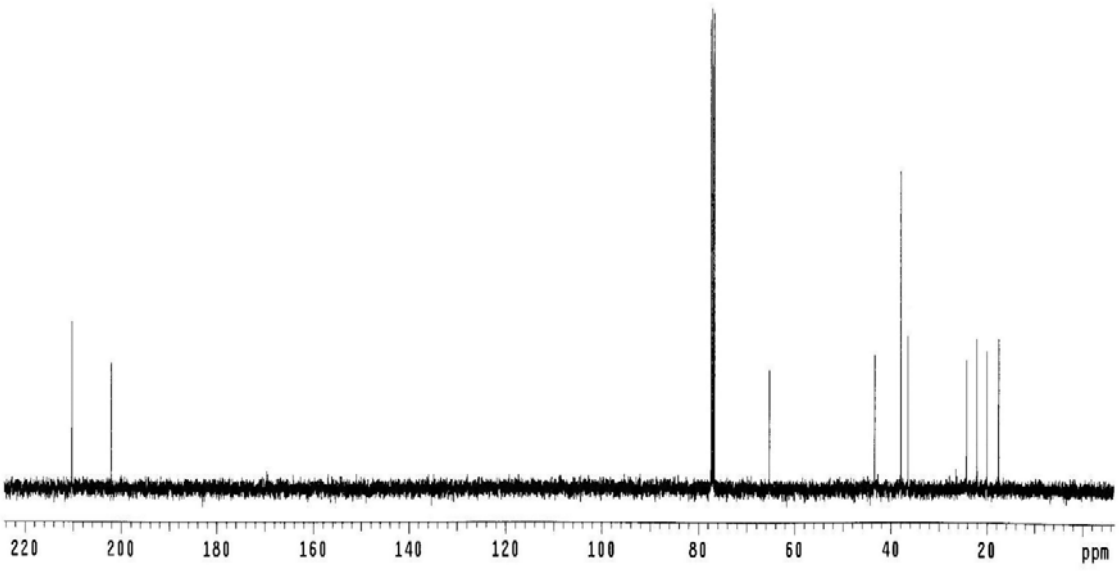
^{13}C NMR of **4.21b**



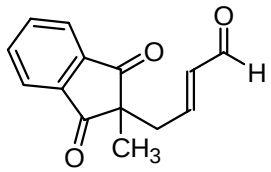
5-(1-Methyl-2,6-dioxocyclohexyl)pentanal 4.21c.Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$); δ 9.70 (t, *J* = 1.7 Hz, 1H), 2.62 (m, 4H), 2.38 (td, *J* = 5.8, 1.7 Hz, 2H), 1.91 (m, 2H), 1.76 (m, 2H), 1.54 (qt, *J* = 7.4 Hz, 2H), 1.19 (s, 3H), 1.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.2, 202.1, 65.3, 43.4, 37.9, 36.4, 24.2, 22.1, 20.0, 17.5. FTIR (NaCl): 2940, 1721, 1685, 1454, 1419, 1367, 1342, 1224, 1183, 1132, 1106, 1019, 906, 727 cm^{-1}. HRMS: calcd for $C_{12}H_{17}O_3$ [M-1] 209.1178; found 209.1171.



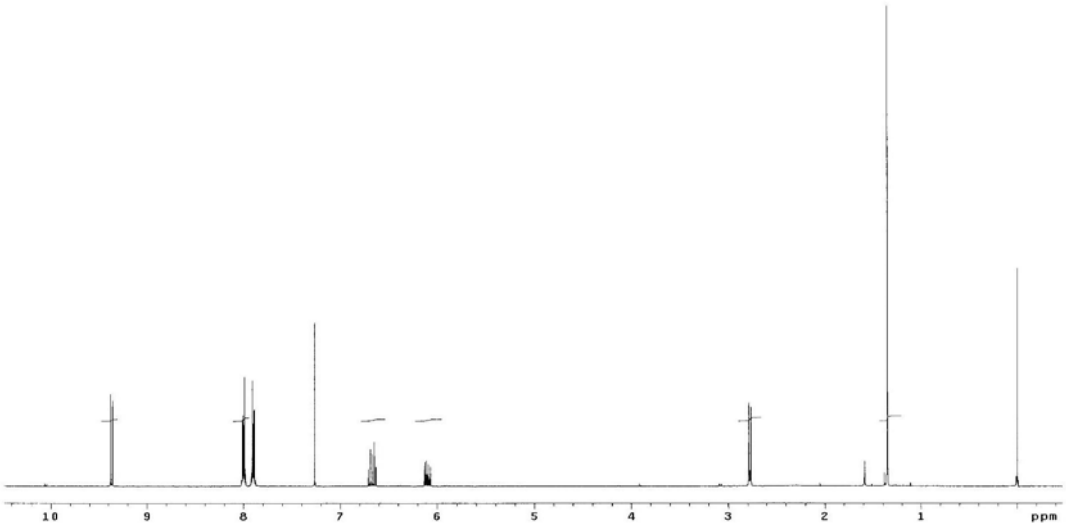
^{1}H NMR of **4.21c**



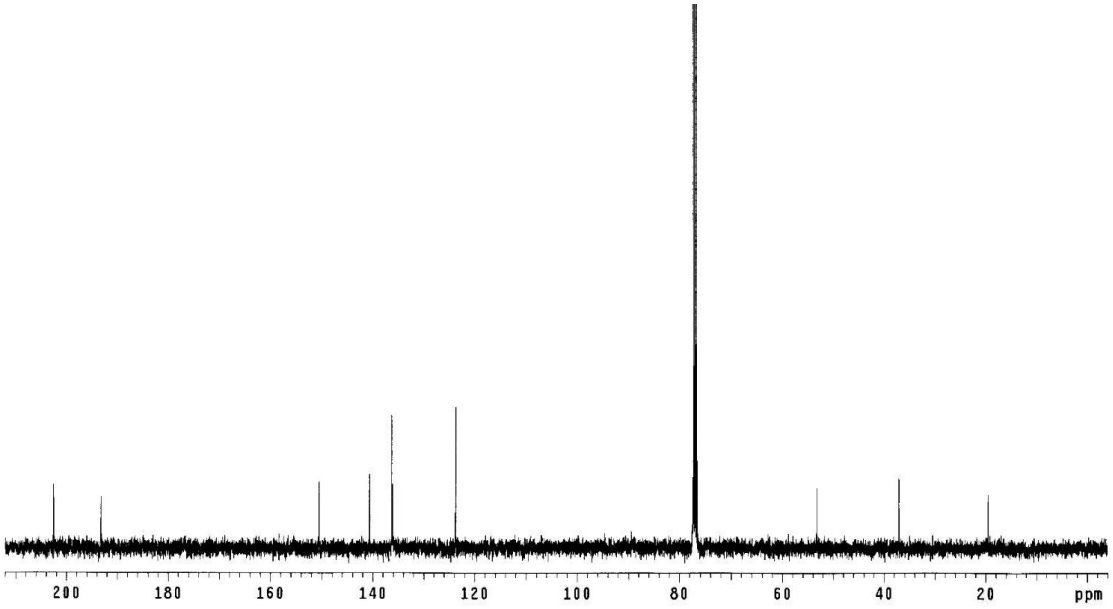
^{13}C NMR of **4.21c**



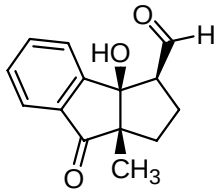
4-(2-Methyl-1,3-dioxoindan-2-yl)but-2-enal 4.22a. White solid ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (d, *J* = 7.9 Hz, 1H), 8.00 (m, 2H), 7.91 (m, 2H), 6.66 (dt, *J* = 15.3, 7.7, Hz, 1H), 6.10 (ddt, *J* = 14.3, 7.9, 1.0 Hz, 1H), 2.77 (dd, *J* =7.9, 1.4 Hz, 2H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 193.2, 150.5, 140.6, 136.3, 136.1, 123.7, 53.2, 37.1, 19.5. FTIR (NaCl): 3083, 2974, 2924, 2858, 1739, 1700, 1677, 1603, 1266, 974 cm^{-1} HRMS: calcd for $C_{14}H_{13}O_3$ [M+1] 229.0865 found 229.0854. MP 92-94 °C.



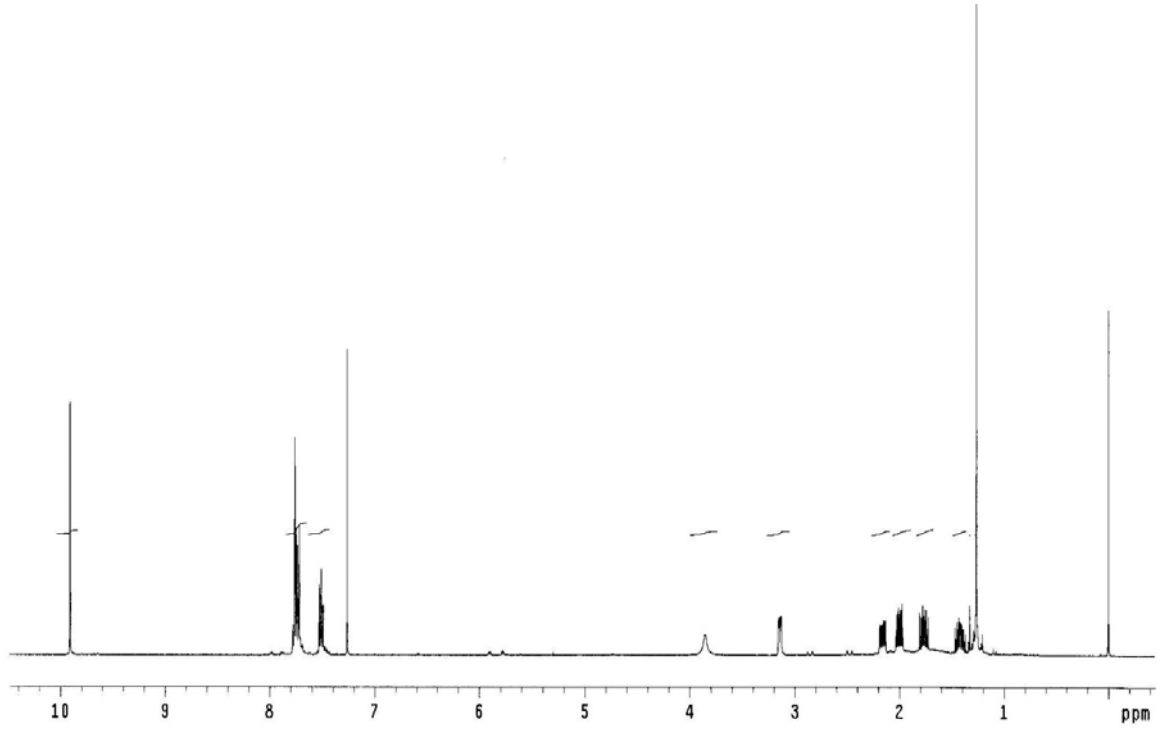
^{1}H NMR of **4.22a**



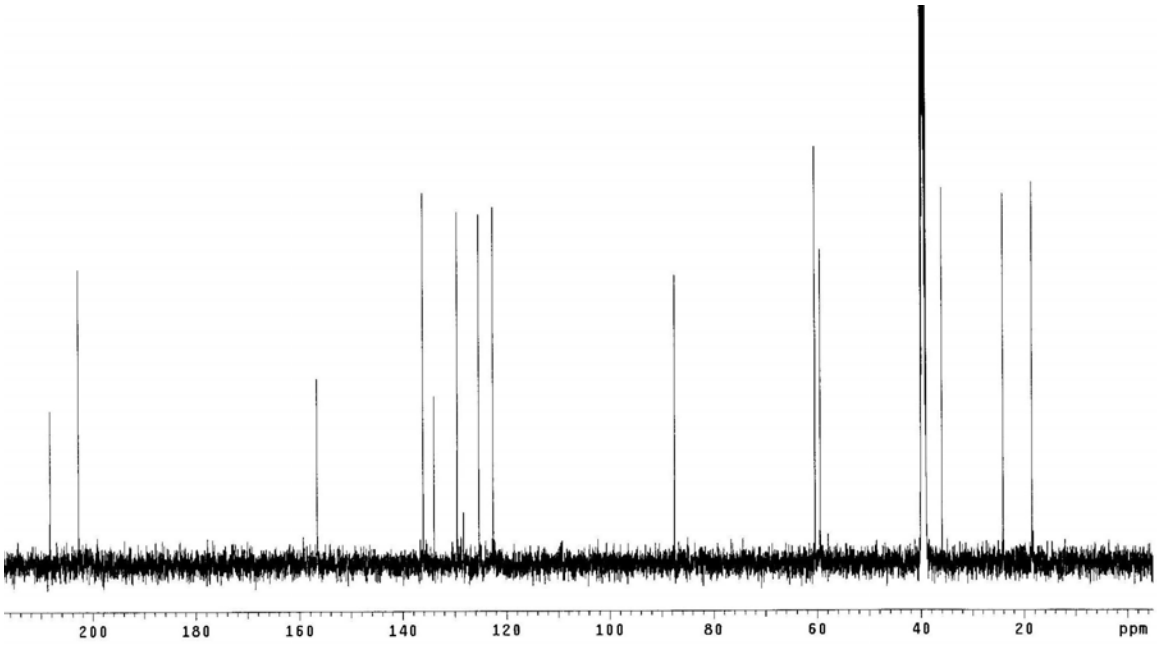
^{13}C NMR of **4.22a**



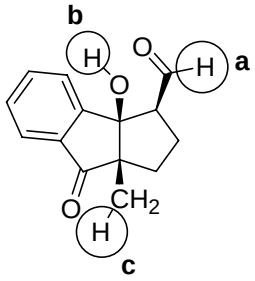
3a-Hydroxy-8a-methyl-8-oxo-1,2,3,3a,8,8a-hexahydrocyclopenta[a]indene-3-carbaldehyde 4.22b-*syn*. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (d, *J* = 1.0 Hz, 1H), 7.75 (m, 3H), 7.55 (m, 1H), 3.83 (s, 1H), 3.14 (dd, *J* = 5.1, 2.4, Hz, 1H), 2.16 (m, 1H), 2.00 (m, 1H), 1.76 (m, 1H), 1.42 (m, 1H), 1.26 (s, 3H). ^{13}C NMR (125 MHz DMSO-d_6): δ 208.3, 202.8, 156.6, 136.1, 134.0, 129.5, 125.3, 122.6, 87.5, 60.4, 59.4, 35.9, 24.1, 18.5. FTIR (NaCl) 3421, 3064, 2940, 2862, 1704, 1603, 1460, 1382, 1297, 1219, 1192, 1017, 932, 726 cm^{-1}. HRMS: calcd for $C_{14}H_{15}O_3$ [M+1] 231.1021; found 231.1015.



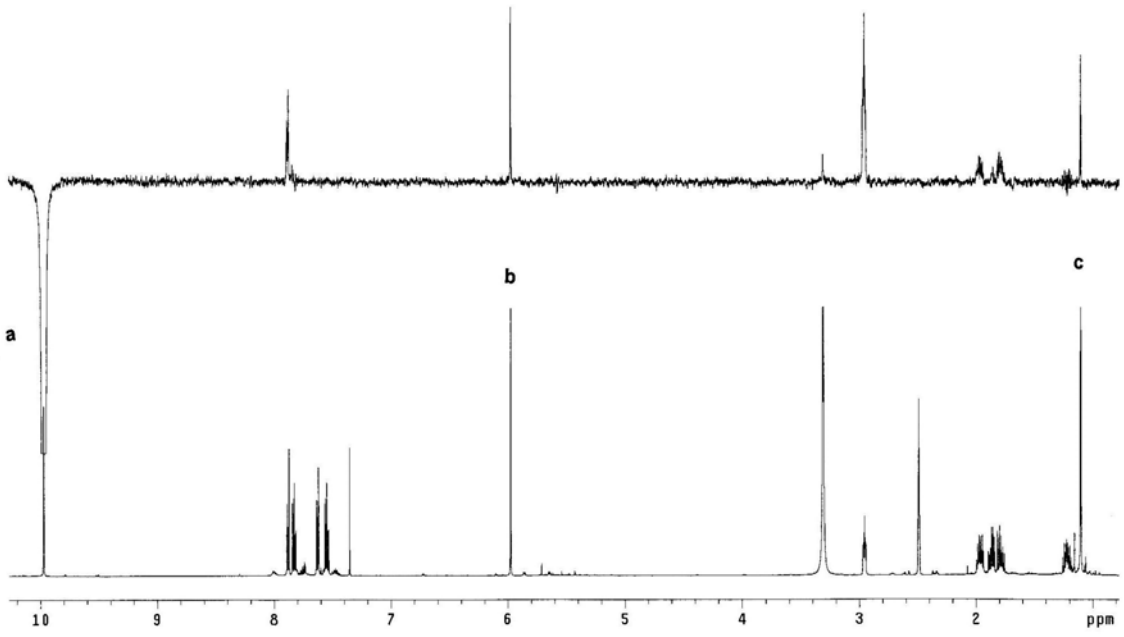
^{1}H NMR of **4.22b-*syn***

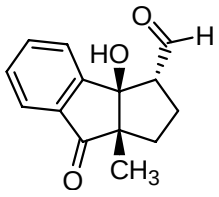


^{13}C NMR of **4.22b-*syn***

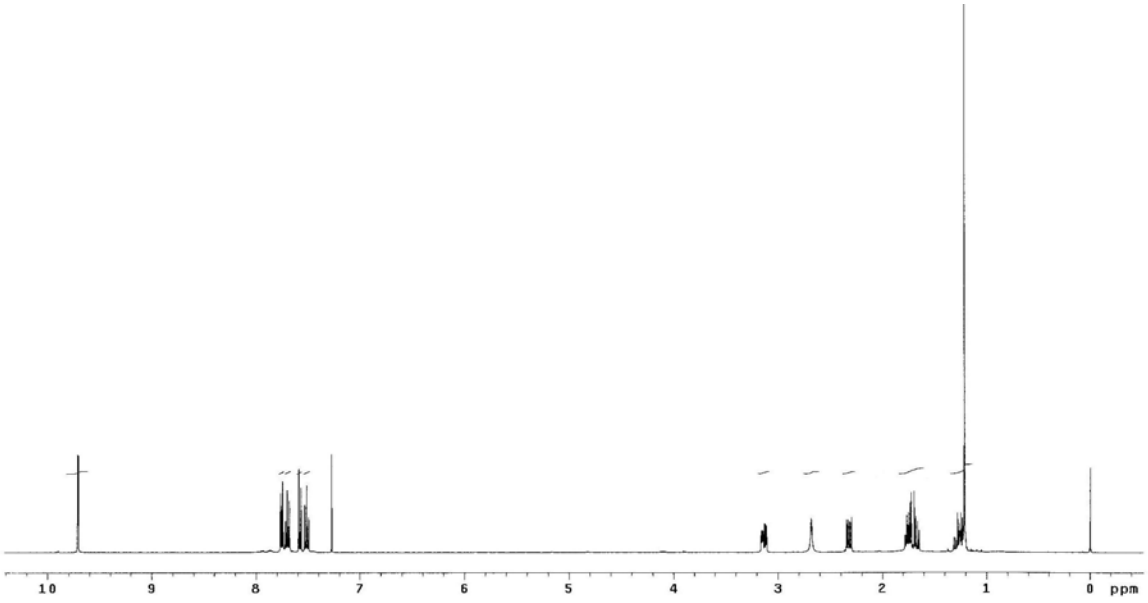


NOE difference (GOESY) (500 MHz, DMSO- d_6) for **4.22b-*syn***

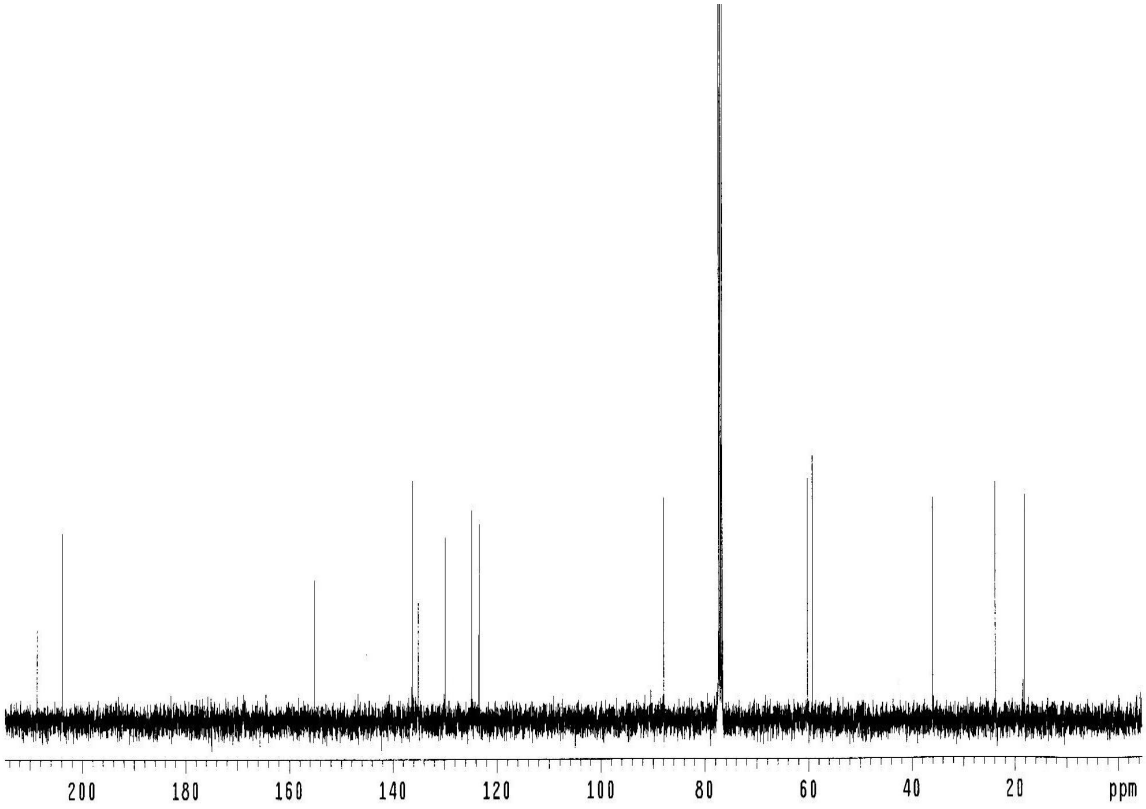




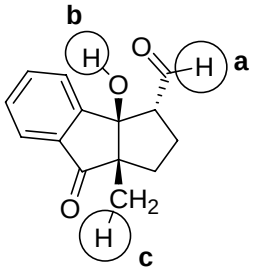
3a-Hydroxy-8a-methyl-8-oxo-1,2,3,3a,8,8a-hexahydrocyclopenta[a]indene-3-carbaldehyde 4.22b-*anti*. Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (d, *J* = 2.4 Hz, 1H), 7.75 (dt, *J* = 8.9, 1.0 Hz, 1H), 7.67 (td, *J* = 6.5, 1.4 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.51 (td, *J* = 6.8, 1.0 Hz, 1H), 3.14 (m, 1H), 2.68 (s, 1H), 2.32 (dd, *J* = 6.5, 5.7 Hz, 1H), 1.71 (m, 2H,) 1.18 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.5, 203.8, 155.1, 136.2, 135.2, 129.8, 124.8, 123.4, 87.9, 60.2, 59.2, 36.0, 23.8, 18.3. FTIR (NaCl): 3440, 2974, 2877, 1704, 1603, 1464, 1258, 1052, 1006, 699 cm^{-1}. HRMS: calcd for $C_{14}H_{15}O_3$ [M+1] 231.1021; found 231.1028.



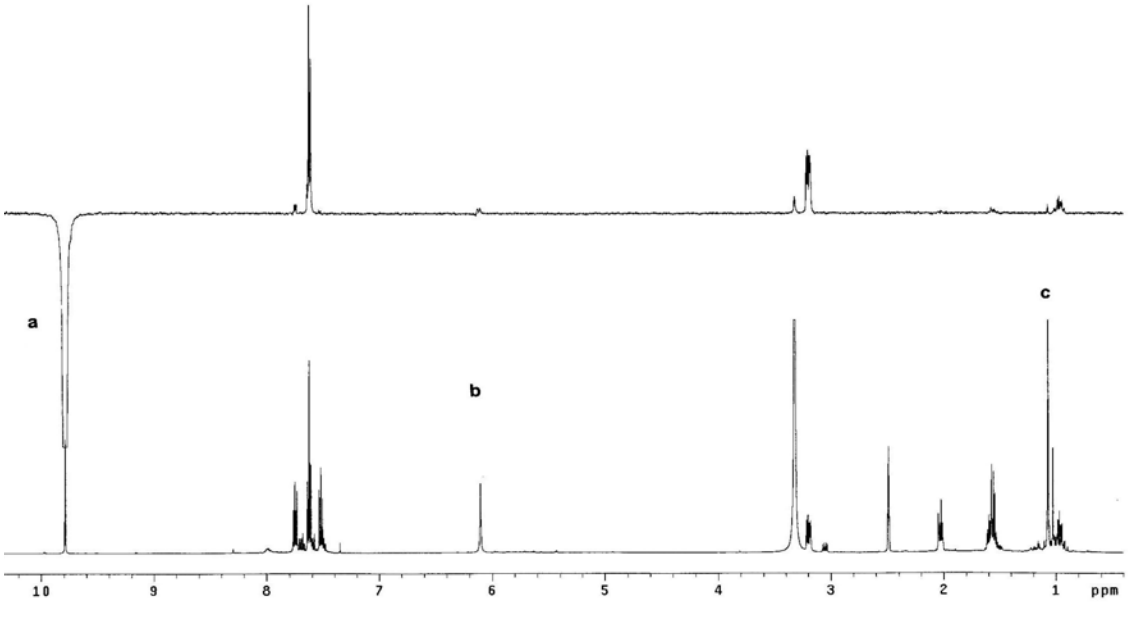
^{1}H NMR of **4.22b-*anti***

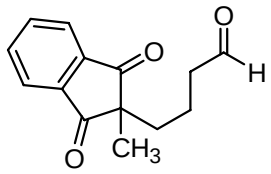


^{13}C NMR of **4.22b-*anti***

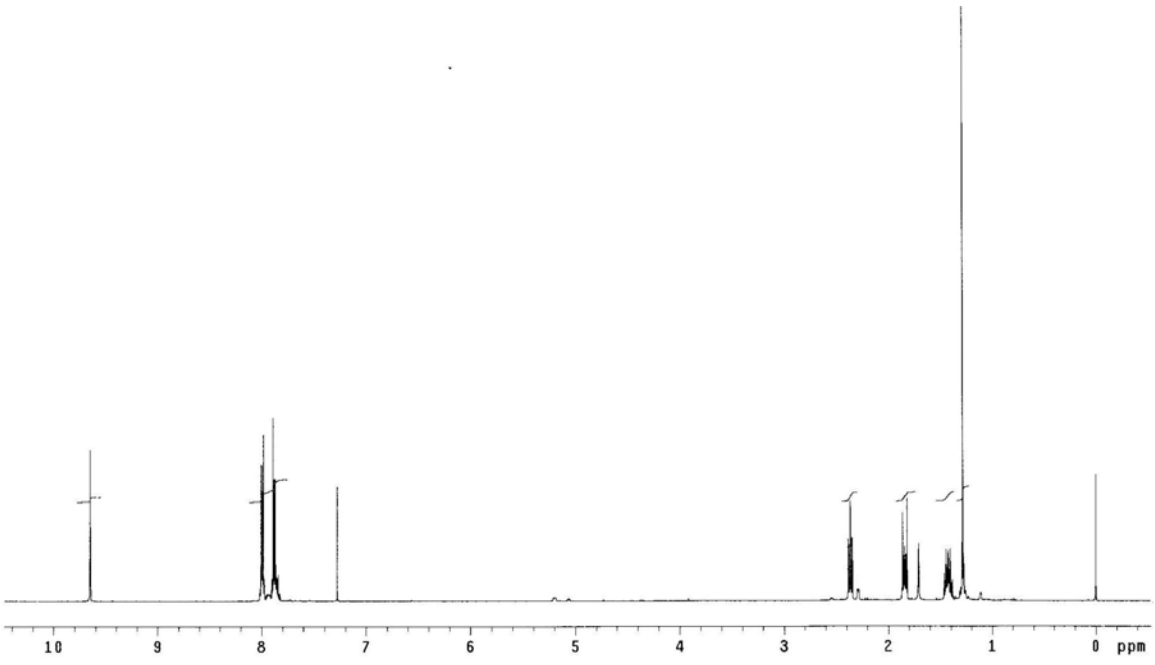


NOE difference (GOESY) (500 MHz, DMSO- d_6) **4.22b-*anti***

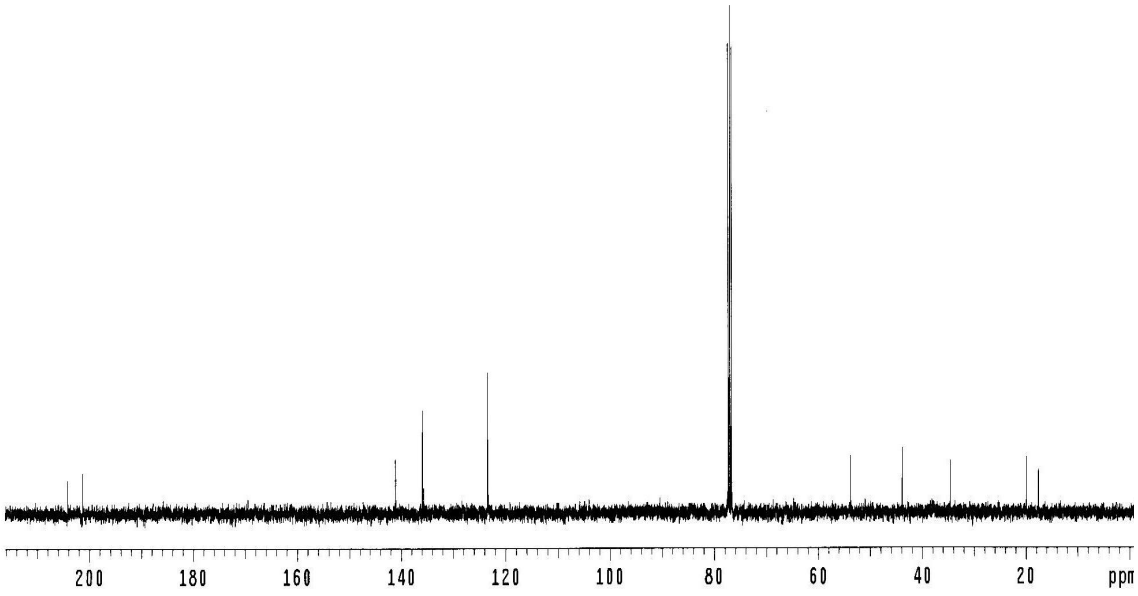




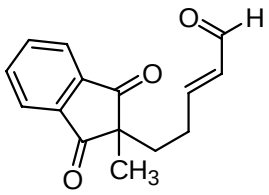
4-(2-Methyl-1,3-dioxo-indan-2-yl)butyraldehyde 4.22c. White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.65 (t, *J* = 1.4 Hz, 1H), 7.99 (m, 2H), 7.89 (m, 2H), 2.36 (td, *J* = 6.2, 1.4 Hz, 2H), 1.84 (m, 2H), 1.42 (m, 2H), 1.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.5, 201.6, 141.4, 136.2, 123.7, 54.0, 44.8, 34.8, 20.1, 17.8. FTIR (NaCl): 3433, 2943, 2839, 2741, 1739, 1700, 1604, 1460, 1374, 1289, 1239, 990, 792, 730 cm^{-1}. HRMS: calcd for $C_{14}H_{15}O_3$ [M+1] 231.10212; found 231.10315. MP 73-75 °C.



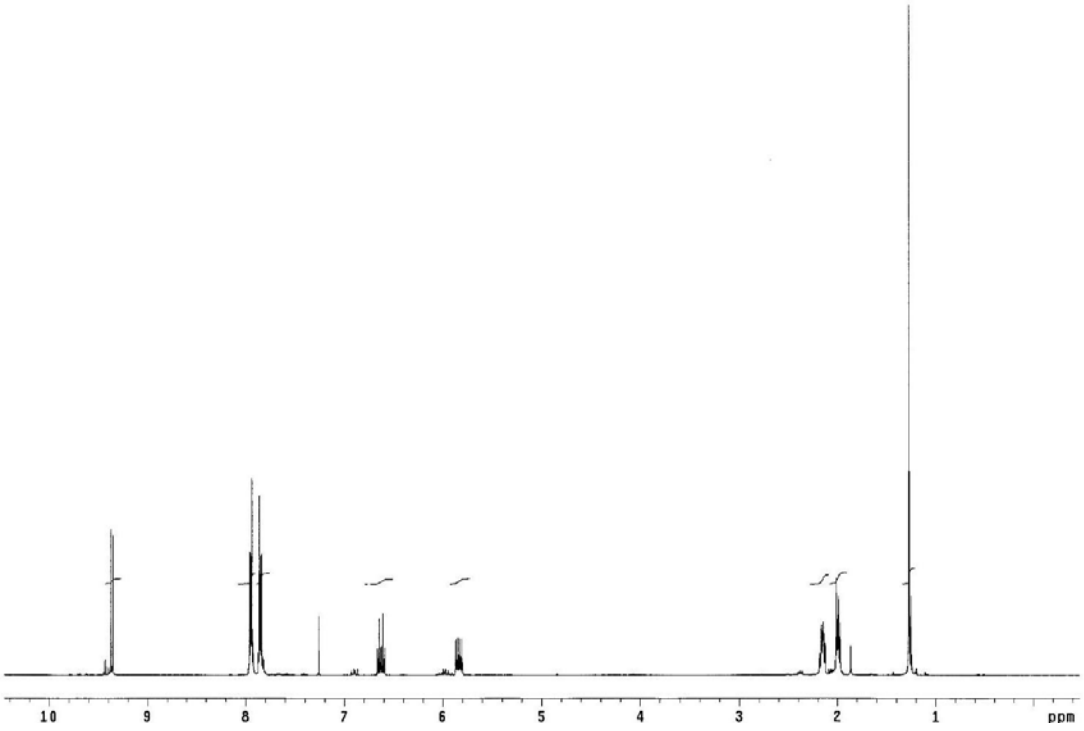
^{1}H NMR of **4.22c**



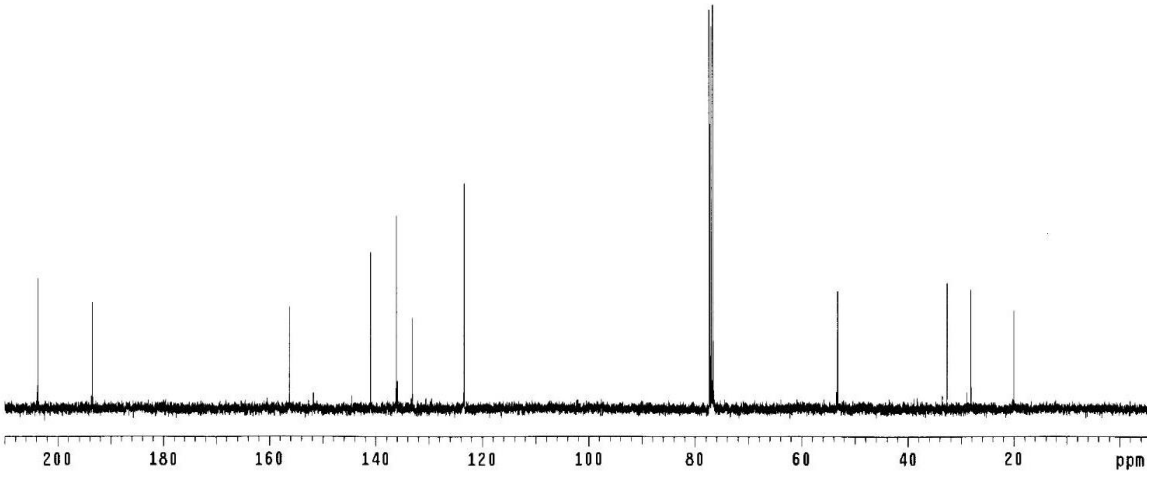
^{13}C NMR of **4.22c**



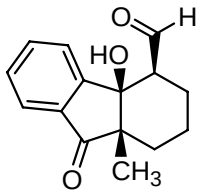
5-(2-Methyl-1,3-dioxoindan-2-yl)pent-2-enal 4.23a. Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$); δ 9.36 (d, *J* = 7.9 Hz, 1H), 7.94 (m, 2H), 7.85 (m, 2H), 6.62 (dt, *J* = 15.7, 6.5 Hz, 1H), 5.84 (ddt, *J* = 15.7, 7.5, 1.7 Hz, 1H), 2.15 (m, 2H), 1.98 (m, 2H) 1.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.7, 193.5, 156.2, 140.9, 136.0, 133.1, 123.4, 53.2, 32.7, 28.1, 20.0. FTIR (NaCl): 3083, 2966, 2920, 2815, 1743, 1701, 1592, 1444, 1266, 1149 982 cm^{-1}. HRMS: calcd for $C_{15}H_{15}O_3$ [M+1] 243.1021; found 243.1024.



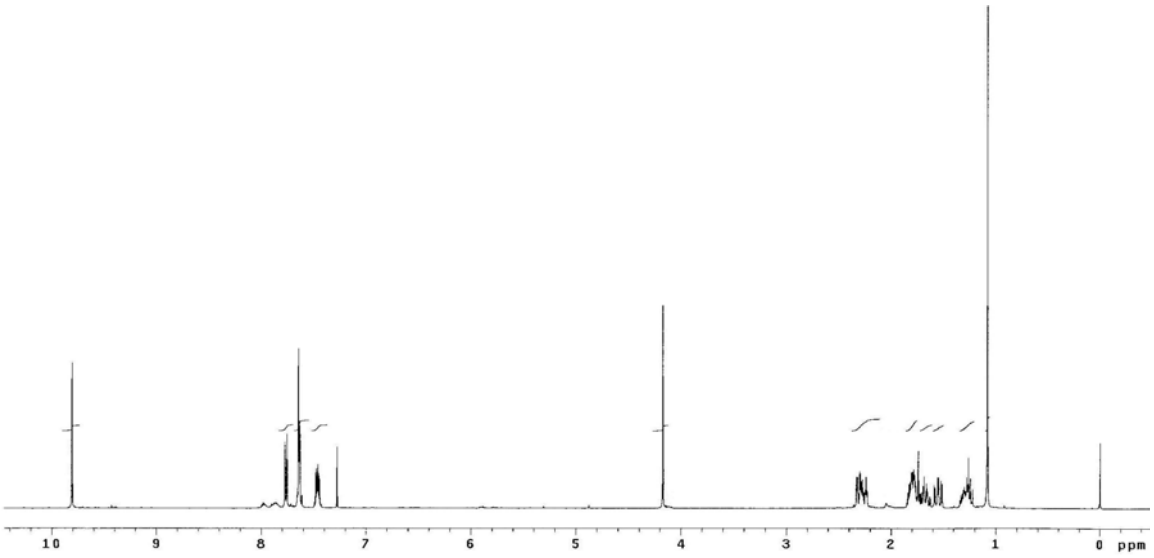
^{1}H NMR of **4.23a**



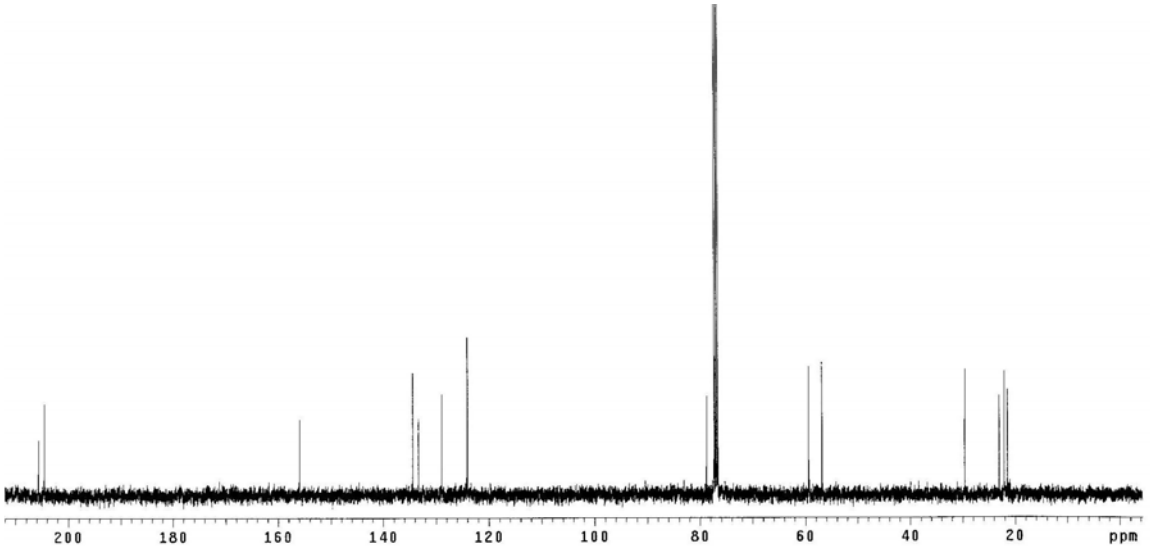
^{13}C NMR of **4.23a**



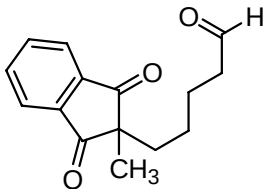
4a-Hydroxy-9a-methyl-9-oxo-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene-4-carbaldehyde 4.23b. Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.81 (d, *J* = 0.2 Hz, 1H), 7.76 (d, 7.5 Hz, 1H), 7.63 (m, 2H), 7.46 (m, 1H), 4.16 (s, 1H), 2.25 (m, 2H), 1.80 (m, 2H), 1.67 (m, 1H), 1.55 (m, 1H), 1.27 (m, 1H), 1.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.7, 204.5, 156.0, 134.5, 133.4, 128.9, 124.1, 78.7, 59.4, 56.9, 29.6, 23.0, 22.1, 21.5. FTIR (NaCl): 3417, 2944, 2870, 1709, 1611, 1468, 1297, 1204, 1048, 761 cm^{-1}. HRMS: calcd for $C_{15}H_{17}O_3$ [M+1] 245.1178; found 245.1181.



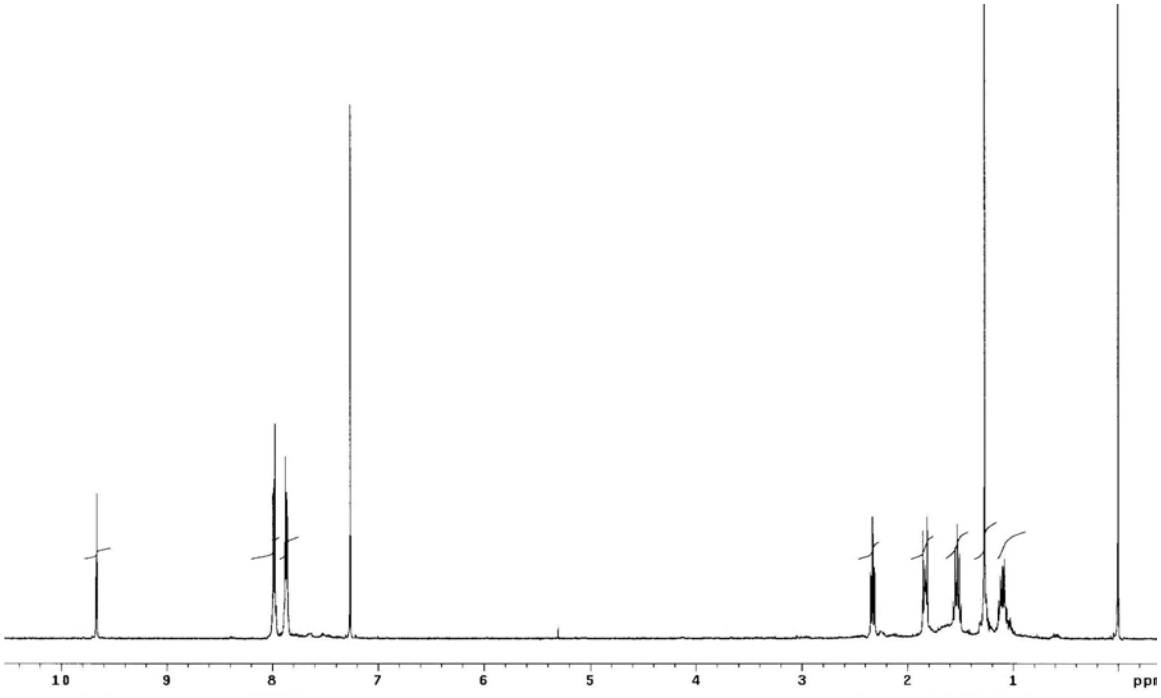
^{1}H NMR of **4.23b**



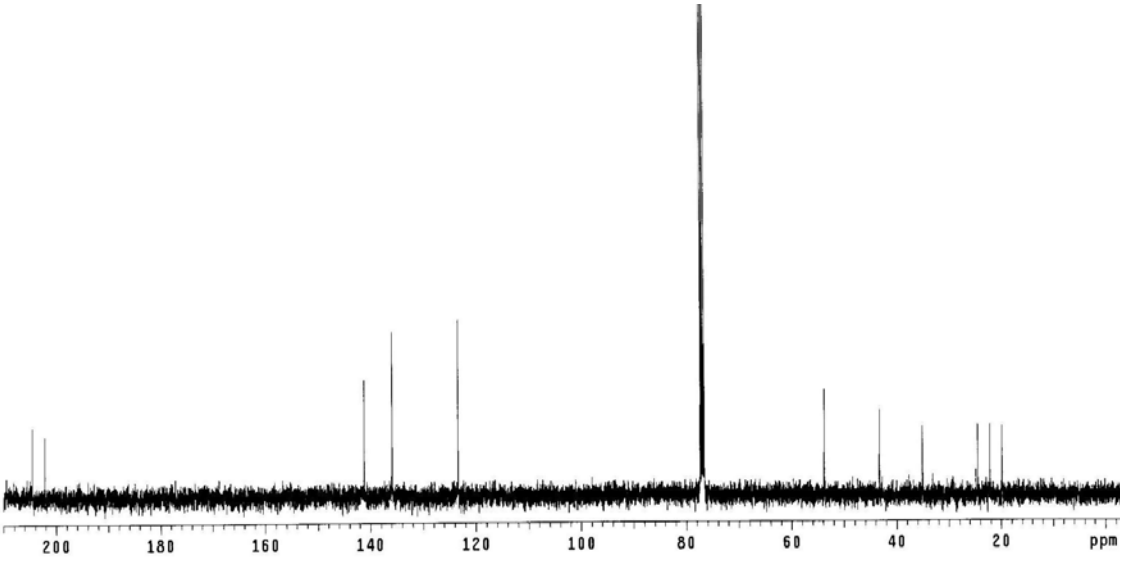
^{13}C NMR of **4.23b**



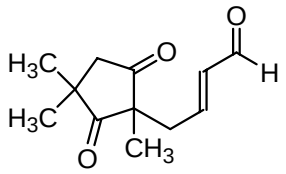
4-(2-Methyl-1,3-dioxo-indan-2-yl)pentanal 4.23c.Yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.63 (t, *J* = 1.7 Hz, 1H), 7.95 (m, 2H), 7.84 (m, 2H), 2.29 (td, *J* =7.5, 1.5 Hz, 2H), 1.80 (m, 2H), 1.49 (qt, *J* = 7.2 Hz, 2H), 1.24 (s, 3H), 1.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.5, 202.1, 141.2, 135.9, 123.4, 53.8, 43.3, 35.1, 24.5, 22.2, 19.8. FTIR (NaCl): 2927, 2850, 1740, 1701, 1598, 1462, 1260, 971, 716 cm^{-1}. HRMS: calcd for $C_{15}H_{17}O_3$ [M+1] 245.1178; found 245.1174.



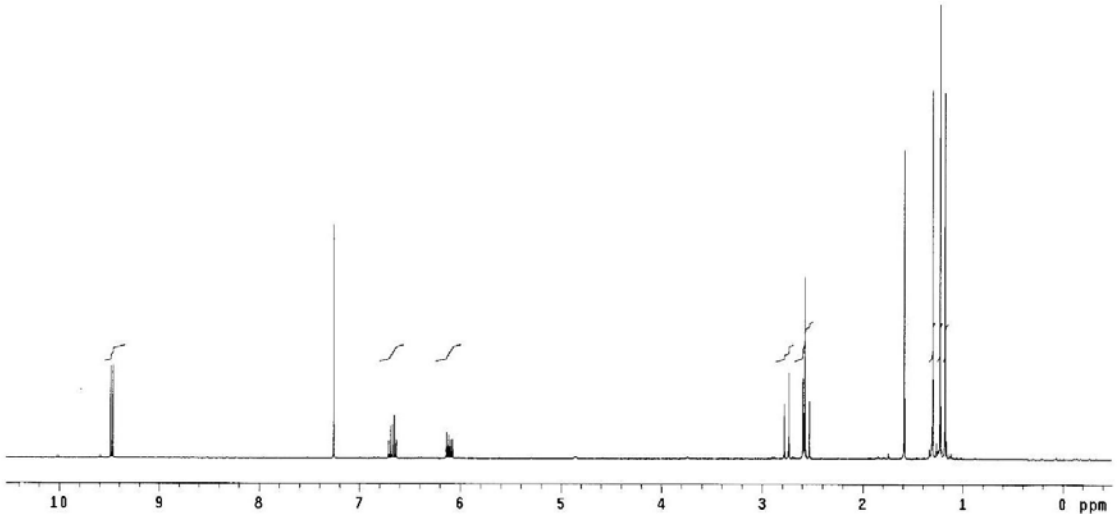
^{1}H NMR of **4.23c**



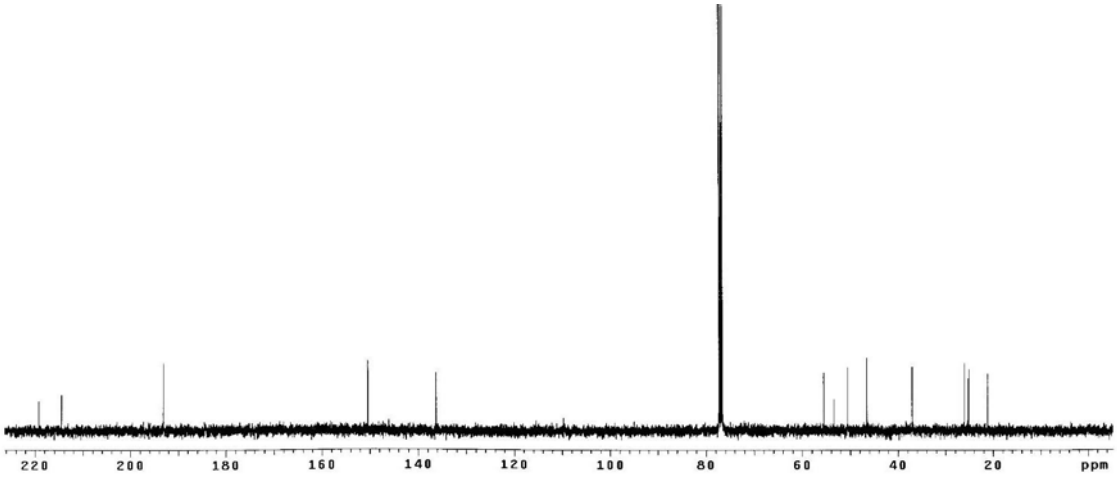
^{13}C NMR of **4.23c**



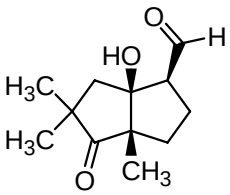
4-(1,3,3-Trimethyl-2,5-dioxo-cyclopentyl)but-2-enal 4.24a. Yellow oil,.^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (d, *J* = 7.9 Hz, 1H), 6.67 (dt, *J* = 15.7, 7.5 Hz, 1H), 6.10 (ddt, *J* = 15.7, 7.9, 1.4 Hz, 1H), 2.75 (A part of AB system, *J* = 18.3 Hz, 1H), 2.58 (dd, *J* = 7.5, 1.0, Hz, 2H), 2.55 (B part of AB system, *J* = 18.3 Hz, 1H) 1.30 (s, 3H), 1.23 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.2, 214.5, 193.1, 150.4, 136.2, 55.5, 50.5, 46.5, 37.0, 26.0, 25.1, 21.1. FTIR (NaCl): 2971, 2928, 2873, 1720, 1689, 1452, 1382, 1223, 1157 1010cm^{-1}; HRMS: calcd for $C_{12}H_{17}O_3$ [M+1] 209.1178; found 209.1180.



^{1}H NMR of **4.24a**

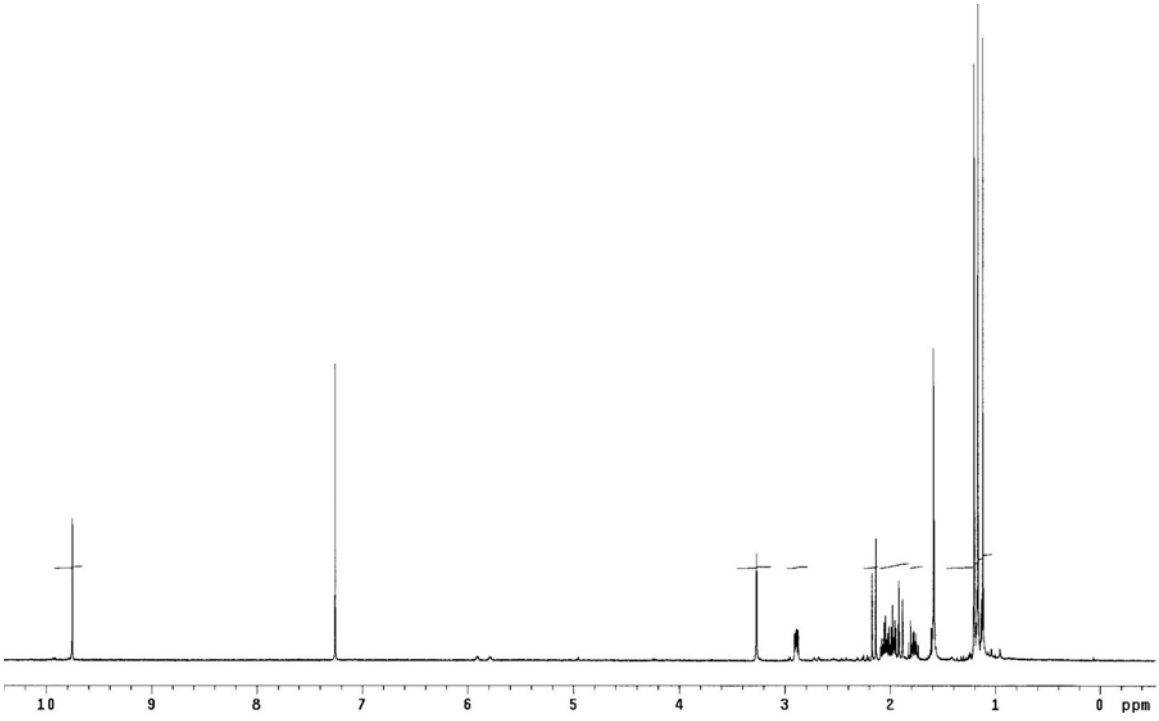


^{13}C NMR of **4.24a**

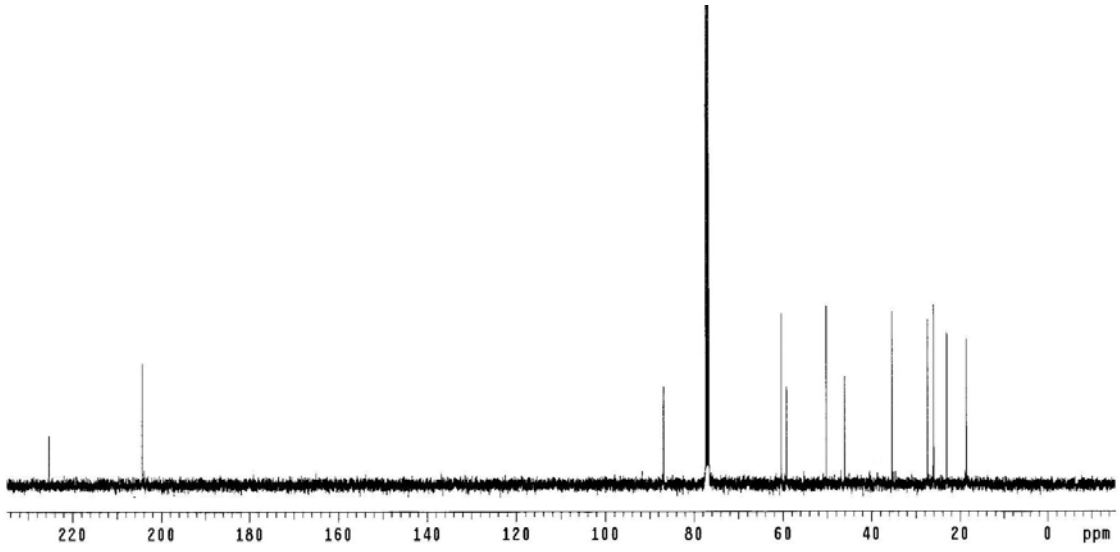


6a-Hydroxy-3a,5,5-trimethyl-4-oxo-octahydropentalene-1-carbaldehyde

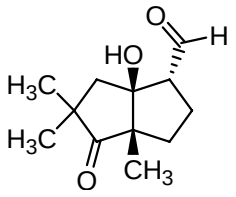
4.24b-***syn***. Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.75 (d, *J* = 1.4 Hz, 1H), 3.27 (s, 1H), 2.89 (m, 1H), 2.15 (m, 1H), 2.00 (m, 3H), 1.78 (m, 1H), 1.59 (m, 1H), 1.19 (s, 3H), 1.16 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 225.3, 204.3, 86.8, 60.4, 59.2, 50.2, 46.0, 35.3, 27.4, 26.0, 23.0, 18.5. FTIR (NaCl): 3479, 2967, 2862, 1716, 1460, 1375, 1180, 1029 cm^{-1}. HRMS calculated [M+1] for $C_{12}H_{19}O_3$ 211.13342; found 211.13328.



^{1}H NMR of **4.24b-*syn***

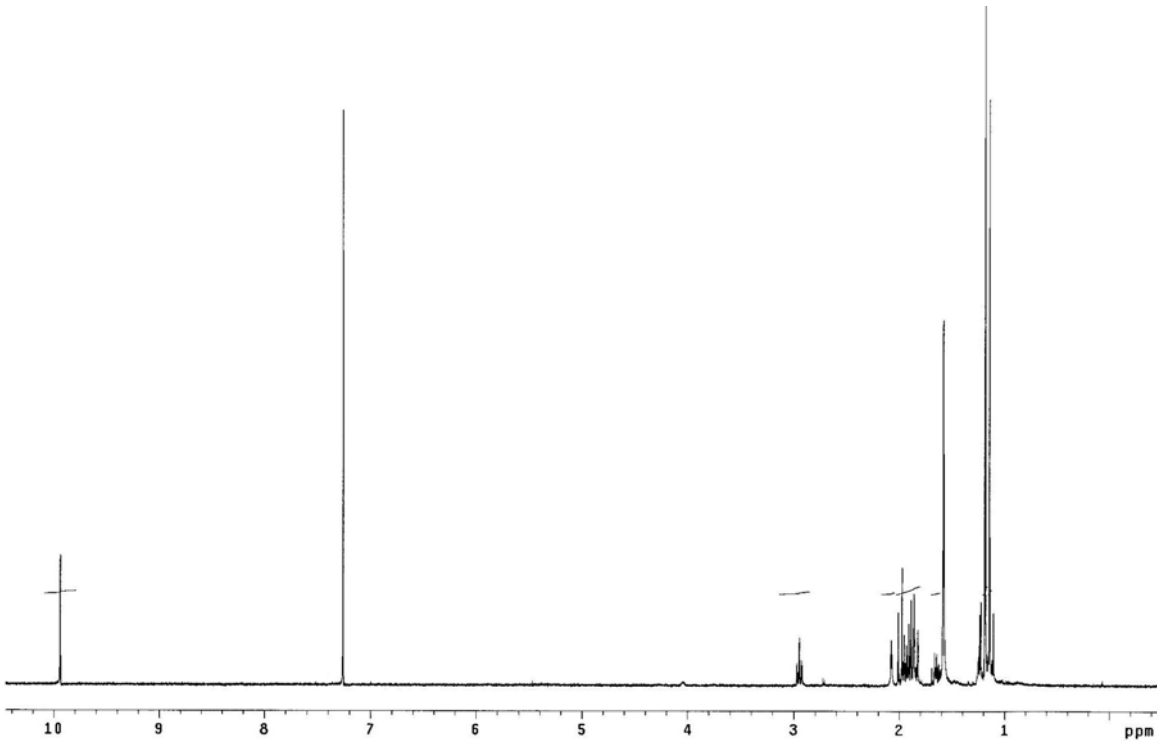


^{13}C NMR of **4.24b-*syn***

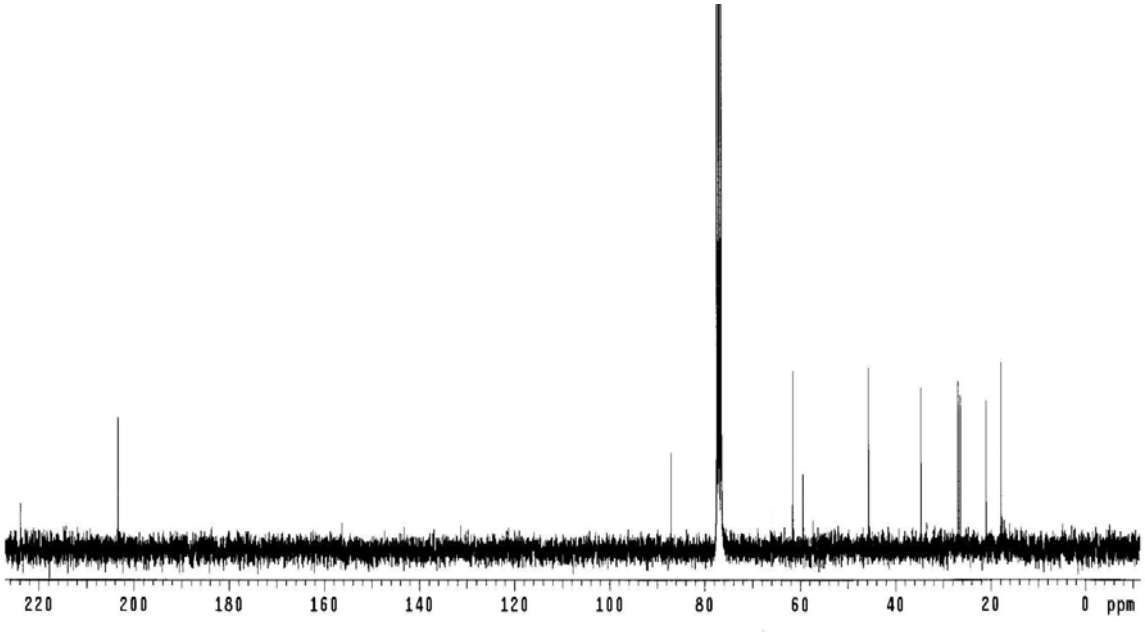


6a-Hydroxy-3a,5,5-trimethyl-4-oxo-octahydropentalene-1-carbaldehyde

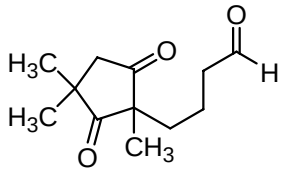
4.24b-*anti*. Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.93 (d, *J* = 1.4 Hz, 1H), 2.94 (t, *J* = 8.5 Hz, 1H), 2.10 (s, 1H), 1.93 (m, 5H), 1.66 (m, 1H), 1.19 (s, 3H), 1.18 (s, 3H) 1.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 223.8, 203.4, 87.0, 61.5, 59.4, 45.6, 45.5, 34.6, 26.8, 26.4, 20.9, 17.8. FTIR (NaCl): 3409, 2966, 2862, 1716, 1448, 1456, 1262, 1176 1033 cm^{-1}. HRMS calculated [M+1] for $C_{12}H_{19}O_3$ 211.13342; found 211.13342.



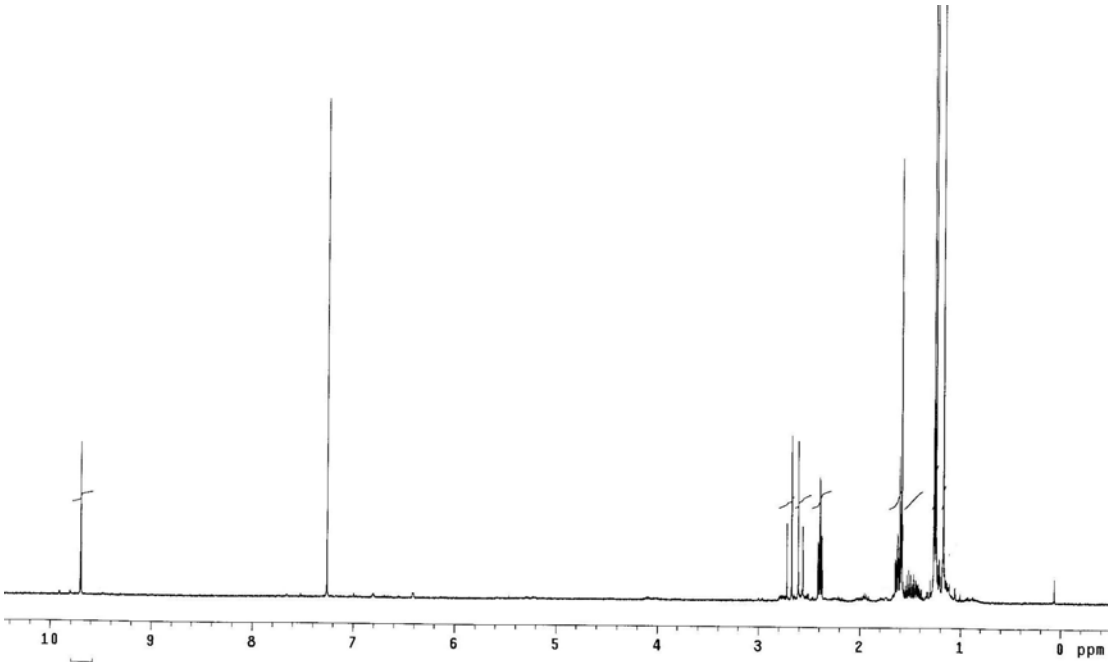
^{1}H NMR of **4.24b-*anti***



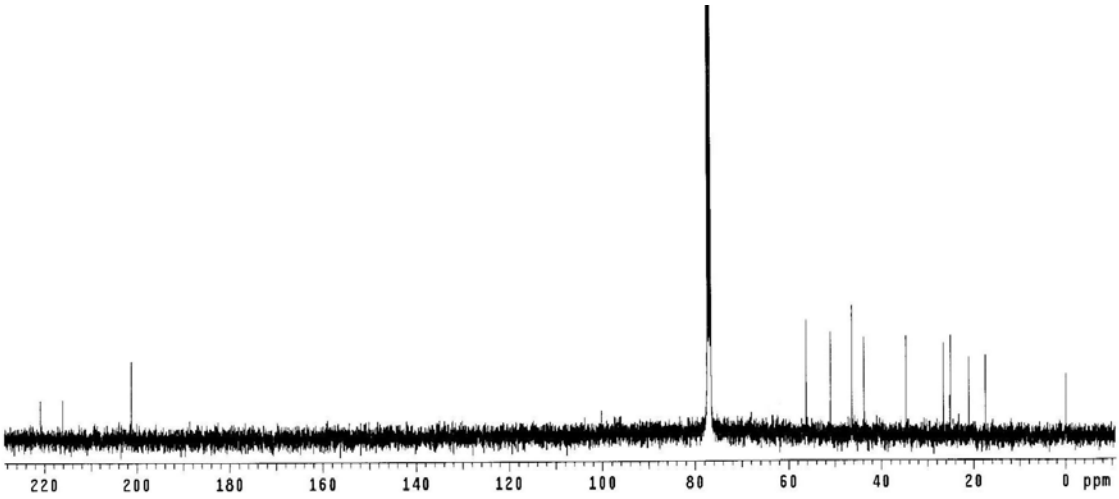
^{13}C NMR of **4.24b-*anti***



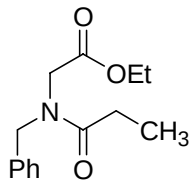
4-(1,3,3-Trimethyl-2,5-dioxo-cyclopentyl)butyraldehyde 4.24c. Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (t, *J* = 1.4 Hz, 1H), 2.69 (A part of AB system, *J* = 18.5 Hz, 1H), 2.59 (B part of AB system, *J* = 18.5 Hz, 1H), 2.39 (td, *J* = 7.2, 1.4 Hz, 2H), 1.63 (m, 2H), 1.40 (m, 2H), 1.26 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.9, 216.1, 201.2, 56.2, 50.9, 46.3, 43.7, 34.4, 26.5, 24.9, 21.0, 17.4. FTIR NaCl: 2971, 2927, 1723, 1636, 1456, 1130, 1010 cm^{-1}. HRMS calculated [M+1] for $C_{12}H_{19}O_3$ 211.13342; found 211.13355.



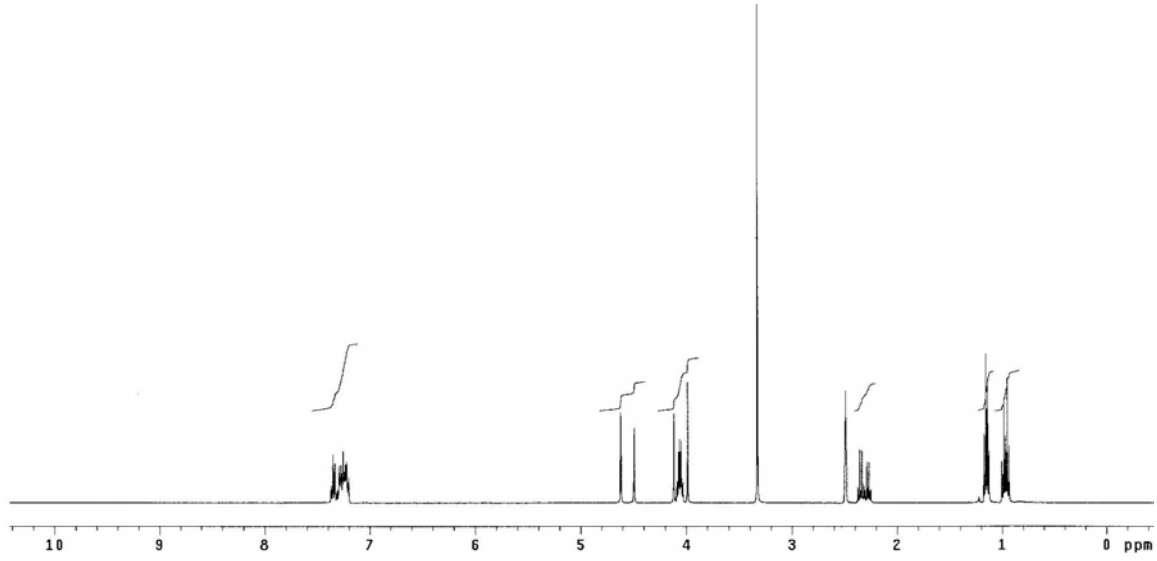
^{1}H NMR of **4.24c**



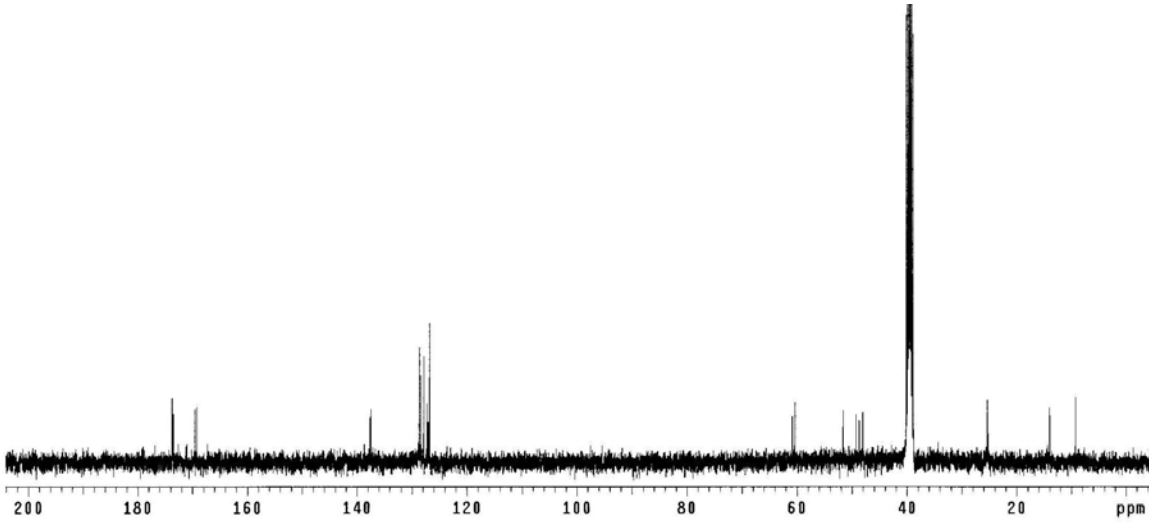
^{13}C NMR of **4.24c**



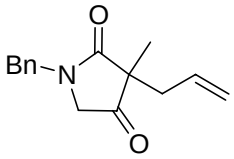
(Benzylpropionylamino)-acetic acid ethyl ester.This compound was isolated as a mixture of rotomers in the ratio (1.2:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29 (m, 5H), 4.62, 4.49 (2s, 2H), 4.12, 3.99 (2s, 2H), 4.06 (m, 2H), 2.31 (2q, *J* = 8.5 Hz, 2H), 1.14 (2t, *J* = 5.5 Hz, 3H), 0.96 (2t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.7, 173.5, 169.6, 169.2, 137.6, 137.4, 128.6, 128.3, 127.8, 127.3, 127.1, 126.8, 60.8, 60.3, 51.6, 49.2, 48.7, 48.0, 25.3, 25.2, 14.0, 13.9, 14.0,13.9, 9.2. FTIR (NaCl): 3064, 3033, 2994, 2947, 1743, 1650, 1471, 1386, 1188, 1033, 904 cm^{-1}. HRMS: calcd for $C_{14}H_{20}NO_3$ [M+1] 250.1443; found 250.1442.



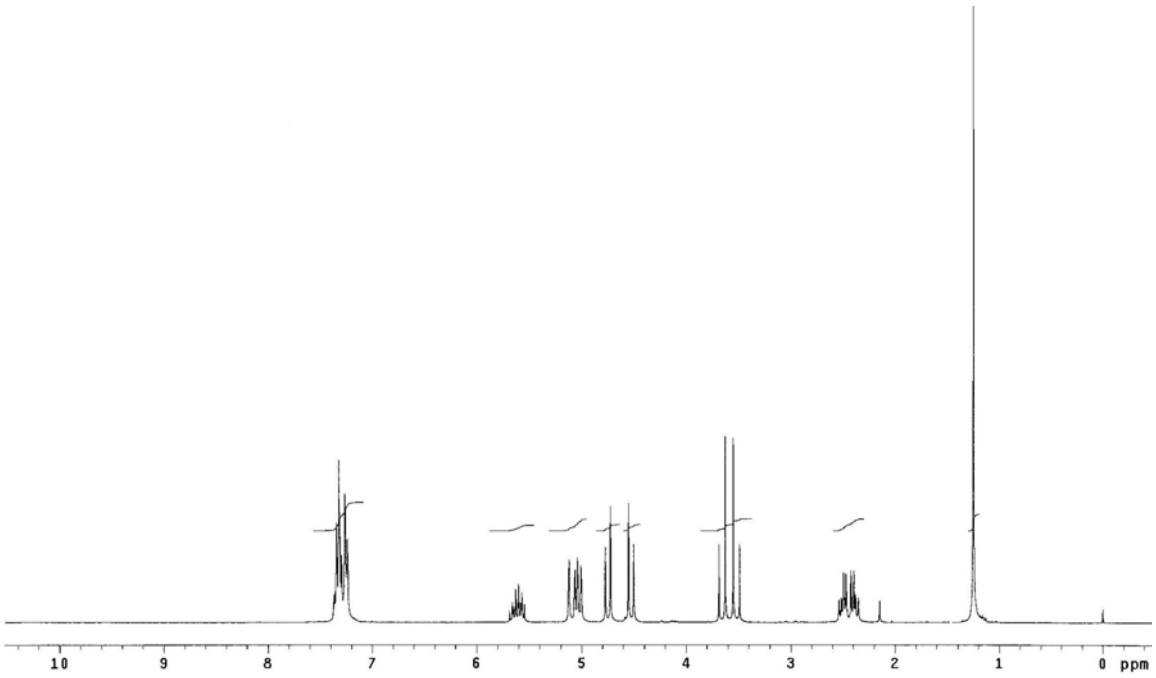
^{1}H NMR of (Benzylpropionylamino)-acetic acid ethyl ester



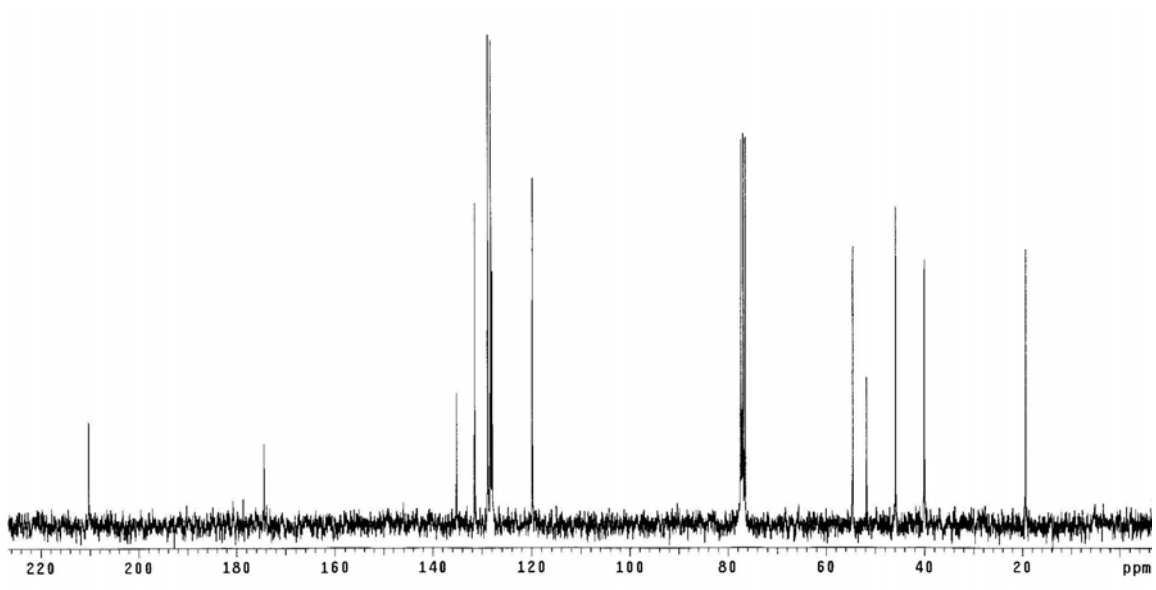
^{1}H NMR of (Benzylpropionylamino)-acetic acid ethyl ester



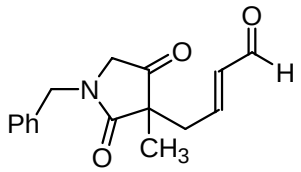
3-Allyl-1-benzyl-3-methylpyrrolidine-2,4-dione.Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 5H), 5.64 (m, 1H), 5.06 (d, *J* = 17.1 Hz, 2H), 4.75 (A part of AB system, *J* = 14.6 Hz, 1H), 4.54 (B part of AB system, *J* = 14.5 Hz, 1H), 3.65 (A part of AB system, d, *J* = 17.8 Hz, 1H), 3.52 (B part of AB system, d, *J* = 17.8 Hz, 1H), 2.44 (m, 2H), 1.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.2, 174.4, 135.1, 131.5, 128.9, 128.3, 128.0, 119.8, 54.6, 51.8, 45.8, 40.0, 19.4. FTIR (NaCl): 3064, 3033, 2967, 2920, 1775, 1689, 1464, 1409, 1250, 1006, 920 cm^{-1}. HRMS: calcd [M+1] for $C_{15}H_{18}NO_2$ 244.1337; found 244.1346.



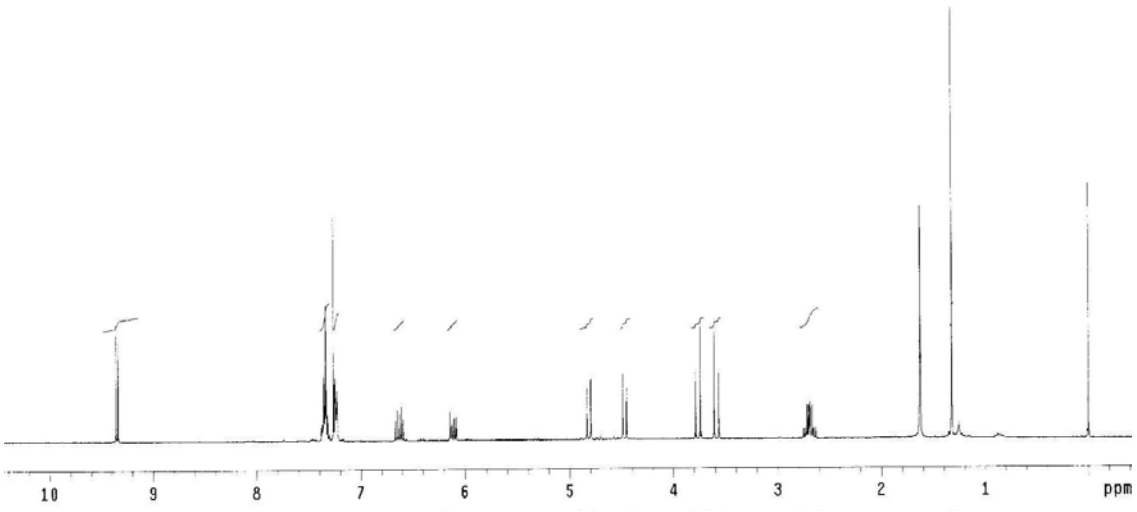
^{1}H NMR of 3-Allyl-1-benzyl-3-methylpyrrolidine-2,4-dione



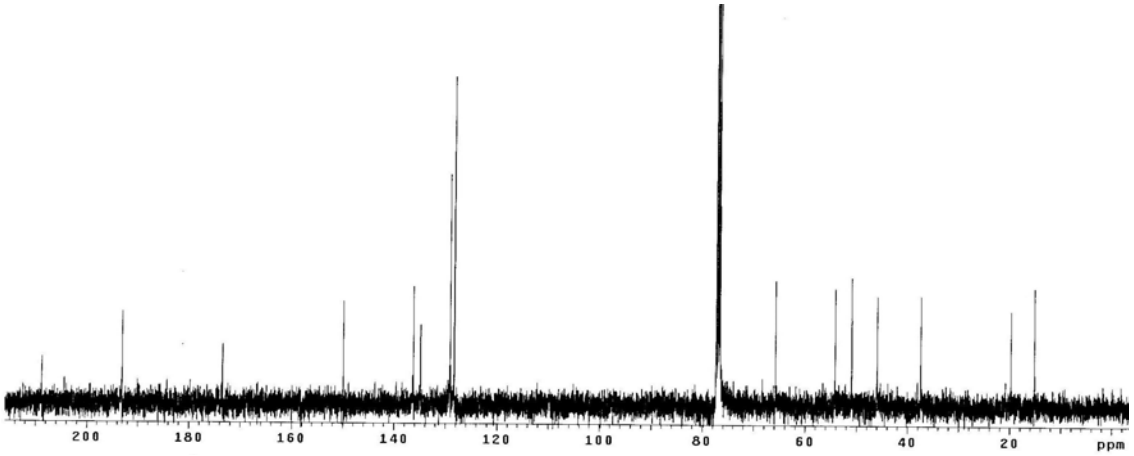
^{13}C NMR of 3-Allyl-1-benzyl-3-methylpyrrolidine-2,4-dione



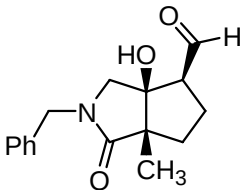
4-(1-Benzyl-3-methyl-2,4-dioxopyrrolidin-3-yl)but-enal 4.25a. Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35 (d, *J* = 7.9 Hz, 1H), 7.35 (m, 3H), 7.24 (m, 2H), 6.63 (td, *J* = 15.4, 7.5 Hz, 1H), 6.11 (ddt, *J* = 15.7, 7.9, 1.4, Hz, 1H), 4.81 (A part of AB system, *J* = 14.7 Hz, 1H), 4.47 (B part of AB system, *J* = 14.7 Hz, 1H) 3.76 (A part of AB system, *J* = 18.1, 1H), 3.58 (B part of AB system *J* = 18.1 Hz, 1H) 2.68 (m, 2H), 1.32 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 208.8, 193.1, 173.4, 149.9, 136.3, 134.8, 129.1, 128.3, 65.8, 54.2, 50.9, 46.0, 37.4, 19.8, 15.2. FTIR (NaCl): 3033, 2928, 2847, 2746, 1775, 1678, 1452, 1413, 1266, 1157, 975 cm^{-1}. HRMS: calcd for $C_{16}H_{18}NO_3$ [M+1] 272.1287; found 272.1286.



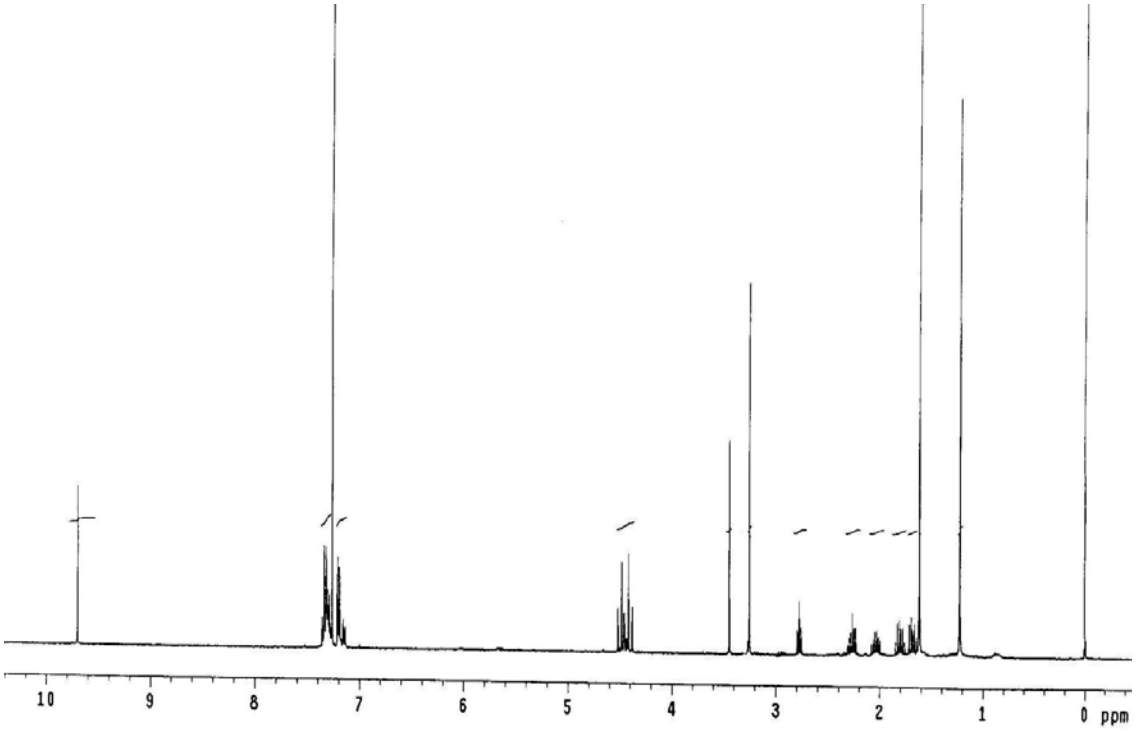
^{1}H NMR of **4.25a**



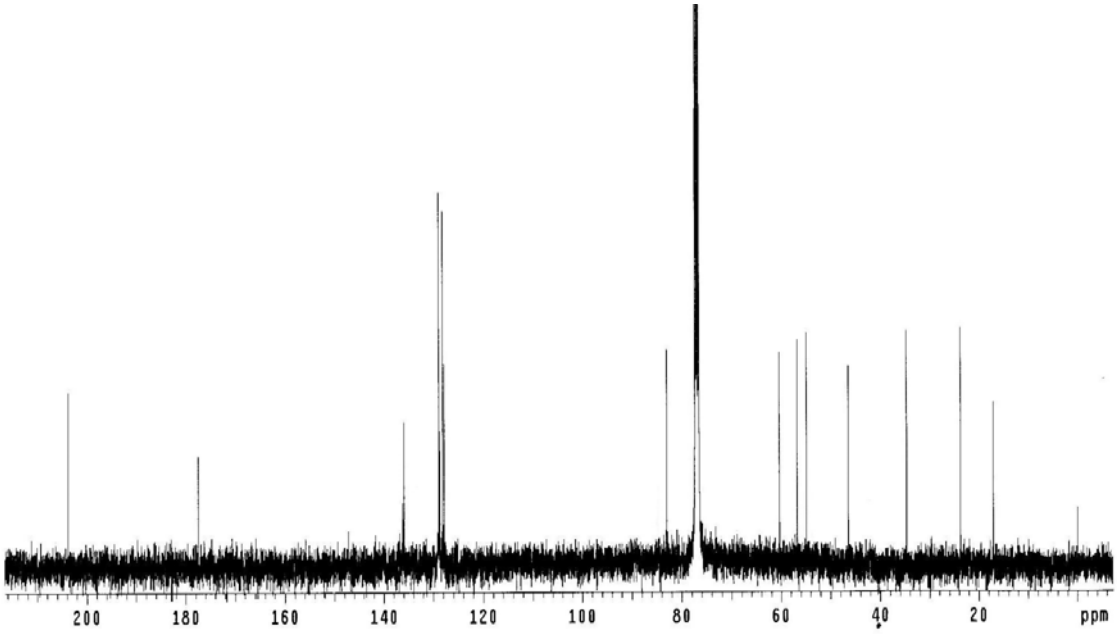
^{13}C NMR of **4.25a**



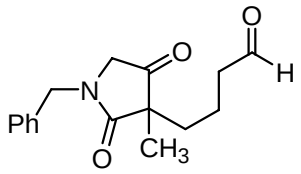
2-Benzyl-3a-hydroxy-6a-methyl-1oxo-octahydrocyclopenta[*c*]pyrrole-4-carbaldehyde 4.25b. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (d, *J* = 1.0 Hz, 1H), 7.31 (m, 3H), 7.17 (m, 2H), 4.45 (AB system, 2H), 3.45 (s, 1H), 3.26 (s, 2H), 2.77 (t, *J* = 7.3 Hz, 1H), 2.27 (m, 1H), 2.04 (m, 1H), 1.80 (m, 1H), 1.67 (m, 1H), 1.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.8, 177.5, 135.9, 128.8, 128.7, 128.1, 127.8, 127.8, 83.1, 60.4, 56.8, 54.9, 46.4, 34.7, 23.7, 17.1. FTIR (NaCl): 3390, 2824, 2858, 2365, 2334, 1716, 1666, 1262, 1130 cm^{-1}. HRMS: calcd for $C_{16}H_{20}O_3$ [M+1] 274.1443; found 274.1443.



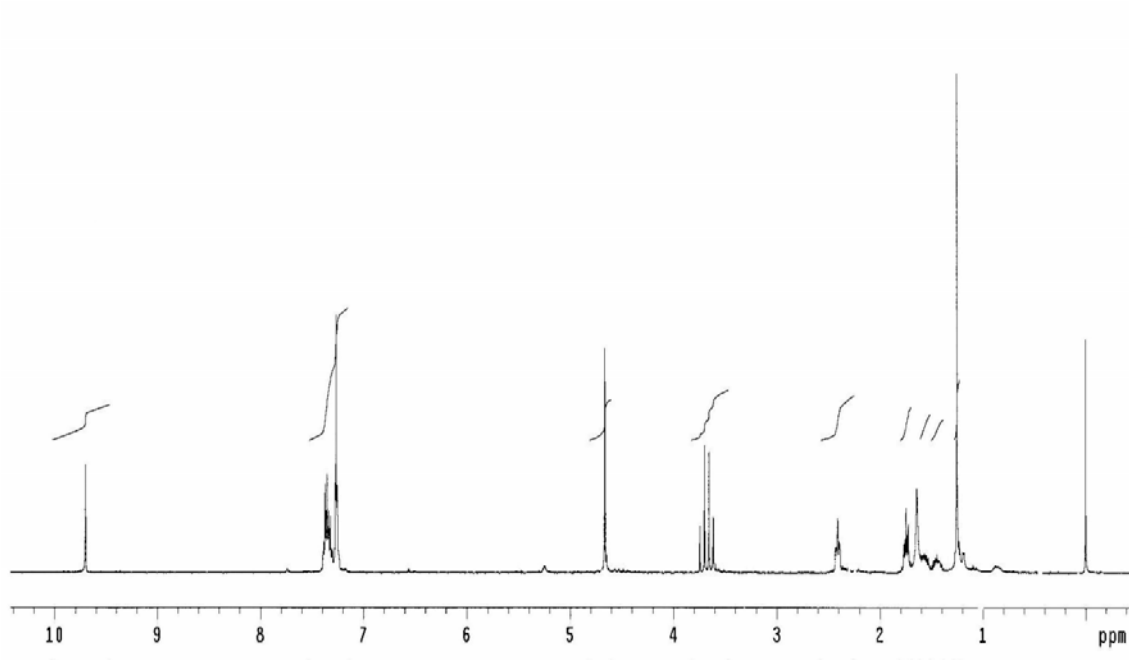
^{1}H NMR of **4.25b**



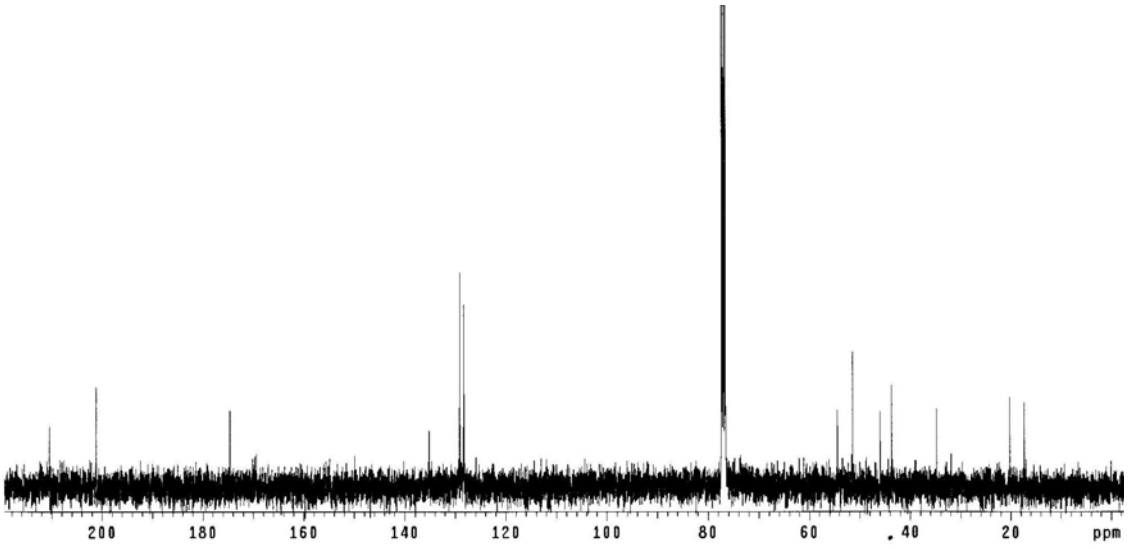
^{13}C NMR of **4.25b**



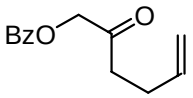
4-(1-Benzyl-3-methyl-2,4-dioxo-pyrrolidin-3-yl)butyraldehyde 4.25c. Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (d, *J* = 1.4 Hz, 1H), 7.31 (m, 5H), 4.66 (s, 2H), 3.72 (A part of AB system, *J* = 18.1 Hz, 1H), 3.63 (B part of AB system d, *J* = 18.7 Hz, 1H), 2.41 (t, *J* = 6.5 Hz, 2H), 1.75 (m, 2H), 1.57 (m, 1H), 1.45 (m, 1H) 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.5, 201.2, 174.7, 135.1, 129.0, 128.4, 128.2, 54.4, 51.4, 45.9, 43.7, 34.8, 20.2, 17.4. FTIR (NaCl): 2967, 2916, 2843, 1777, 1689, 1441, 1262 cm^{-1}. HRMS calculated [M+1] for $C_{16}H_{20}NO_3$ 274.14432; found 274.14460.



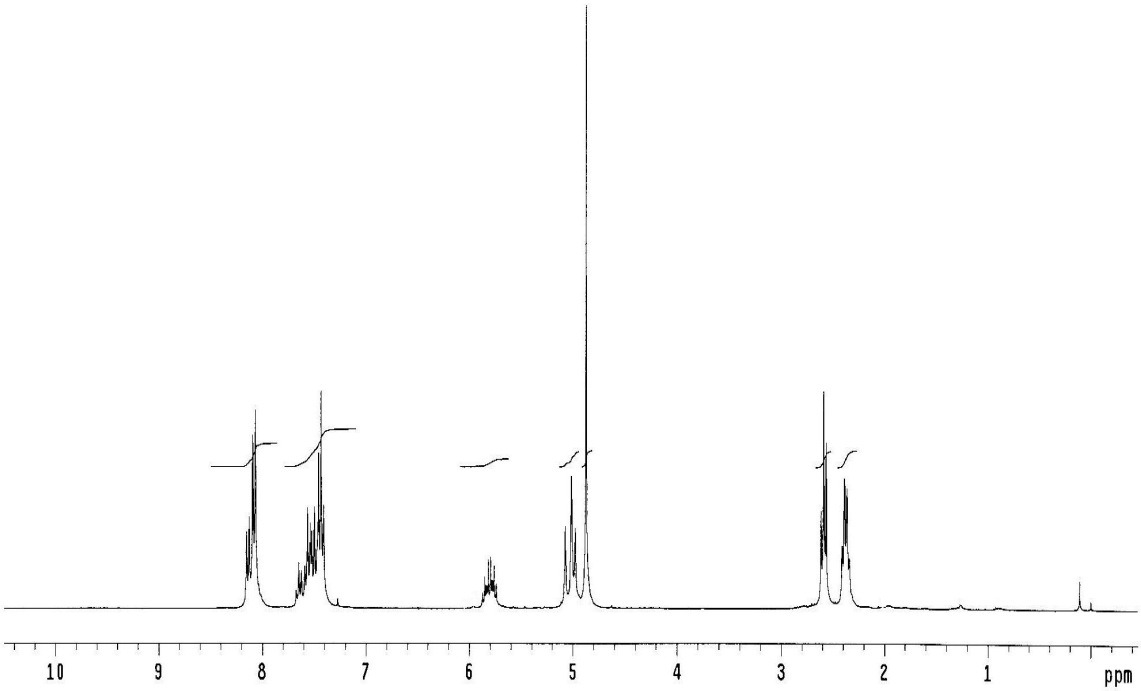
^{1}H NMR of **4.25c**



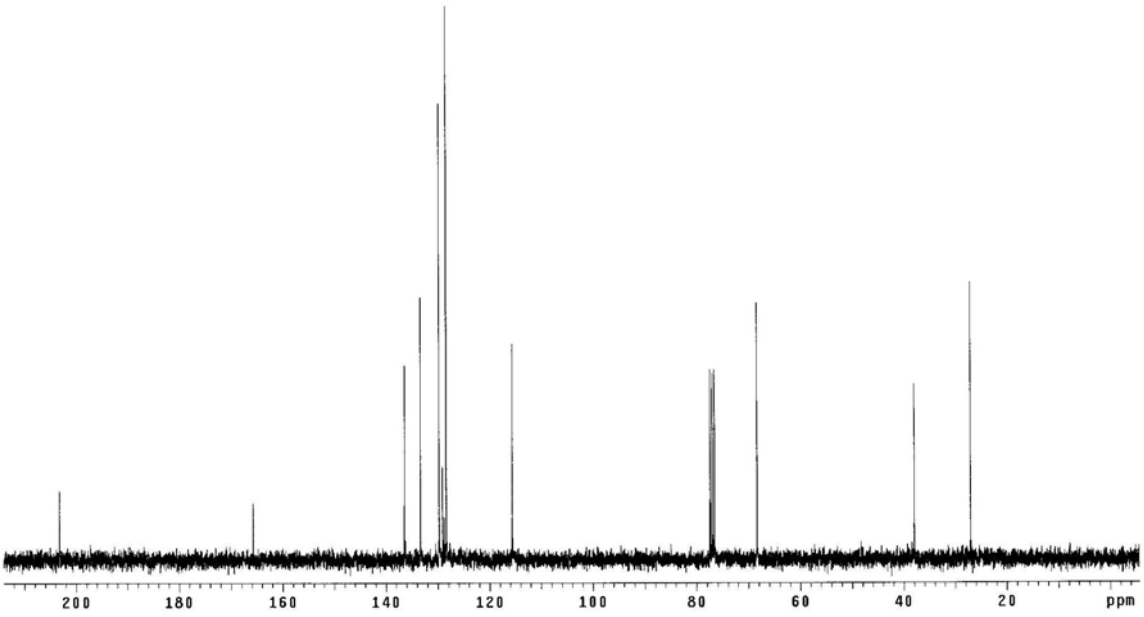
^{13}C NMR of **4.25c**



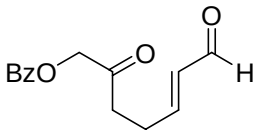
Benzoic acid 2-oxohex-5-enyl ester. Colorless liquid ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (m, 2H), 7.53 (m, 3H), 5.79 (m, 1H), 5.03 (m, 2H), 4.87 (s, 2H), 2.58 (t, *J* = 7.0 Hz, 2H), 2.37 (q, *J* = 6.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.2, 165.8, 136.4, 133.4, 133.4, 129.8, 129.1, 128.8, 115.7, 68.4, 38.0, 27.1. FTIR (NaCl): 3080, 2982, 2912, 1798, 1716, 1608, 1448, 1413, 1278, 1215, 1118, 1076, 982 cm^{-1}. HRMS: calculated for $C_{13}H_{15}O_3$ [M+1] 219.1021; found 219.1024



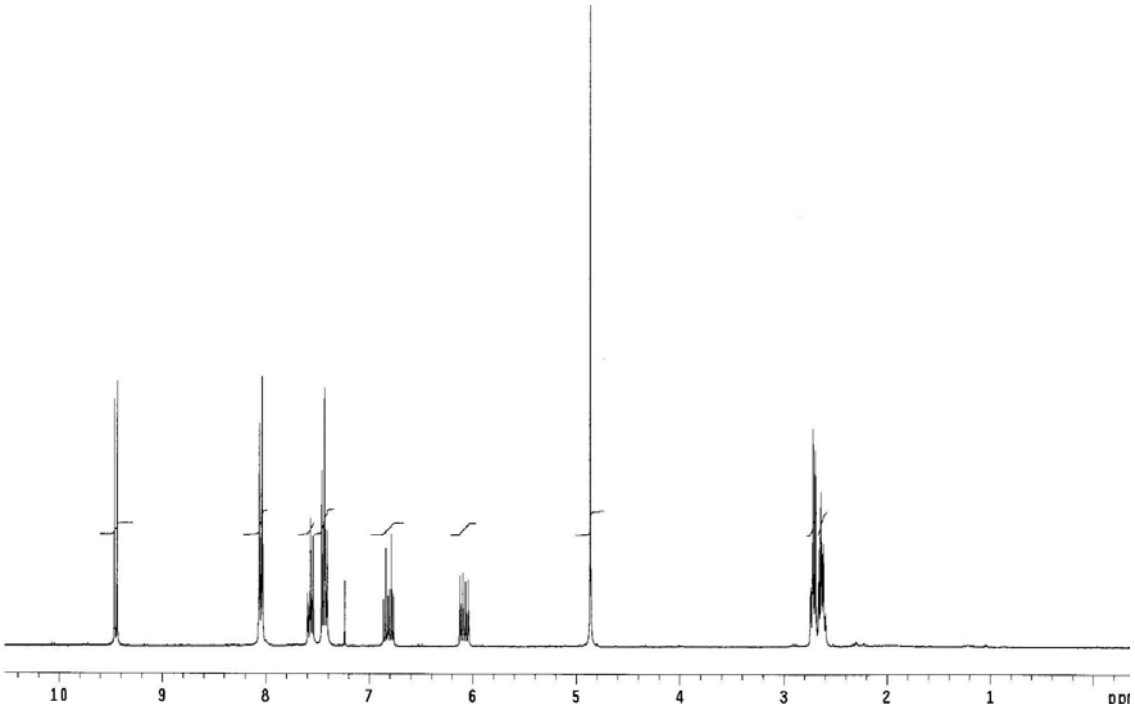
^{1}H NMR of Benzoic acid 2-oxohex-5-enyl ester



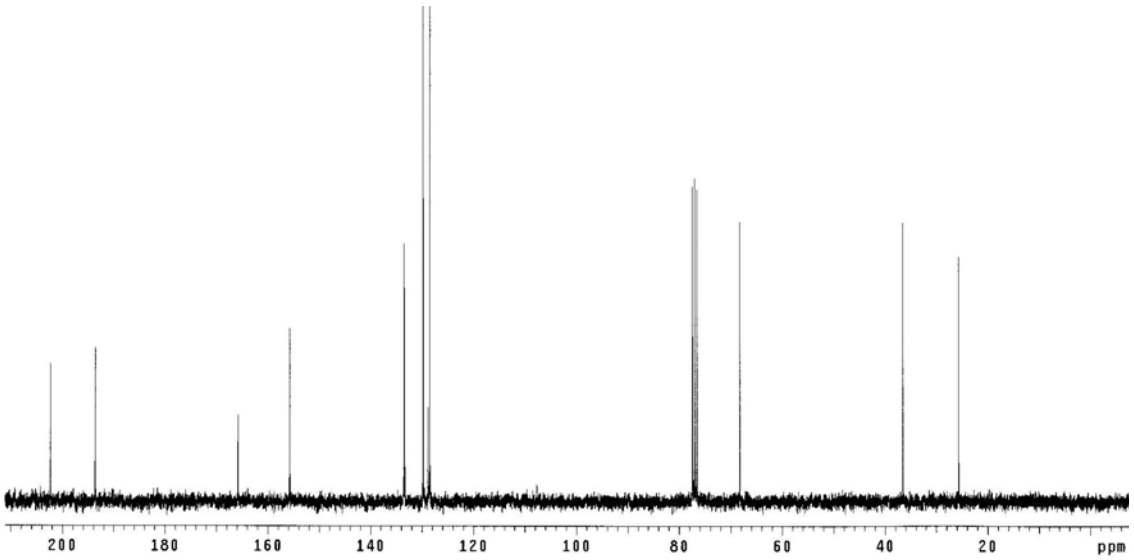
^{13}C NMR of Benzoic acid 2-oxohex-5-enyl ester



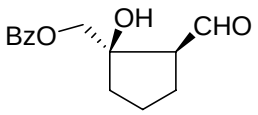
Benzoic acid 2,7-dioxo-hept-5-enyl ester 4.26a. White solid ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (d, *J* = 7.7 Hz, 1H), 8.05 (d, *J* = 5.6 Hz, 2H) 7.56 (m, 1H), 7.43 (t, *J* = 12.0 Hz, 2H), 6.82 (dt, *J* = 6.7, 15.6 Hz, 1H), 6.08 (ddt, *J* =15.9, 7.9, 1.3, Hz, 1H), 4.86 (s, 2H), 2.71 (m, 2H), 2.63 (t, *J* = 5.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 193.6, 165.8, 155.7, 133.5, 133.4, 129.7, 128.8, 128.5, 68.2, 36.5, 25.6. FTIR (NaCl): 3068, 2932, 2815, 2741, 1736, 1681, 1452, 1266, 1130, 1087, 1029, 974 cm^{-1}. HRMS: calcd for $C_{14}H_{15}O_4$ 247.09703 [M+1] found 247.09736. MP 102-104 °C.



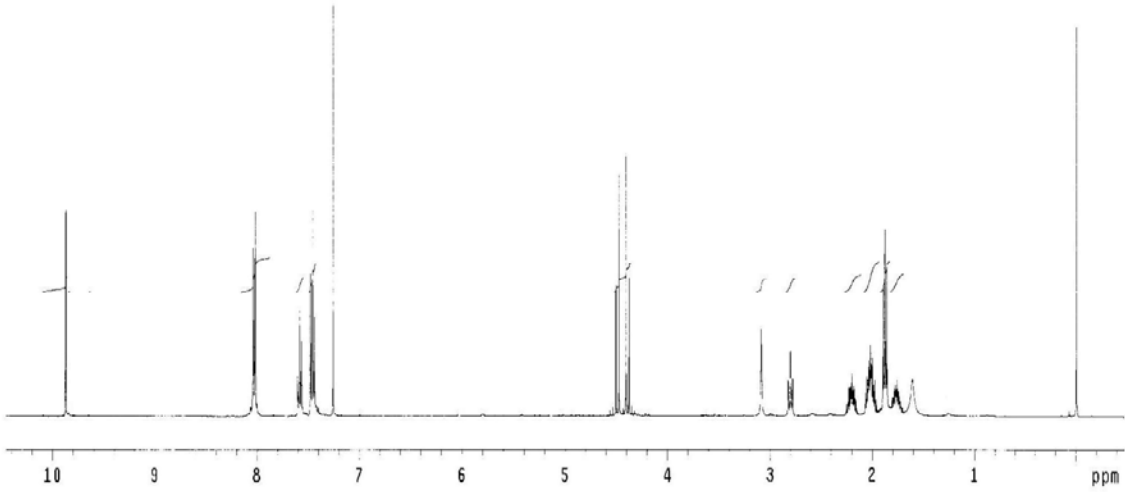
^{1}H NMR of **4.26a**



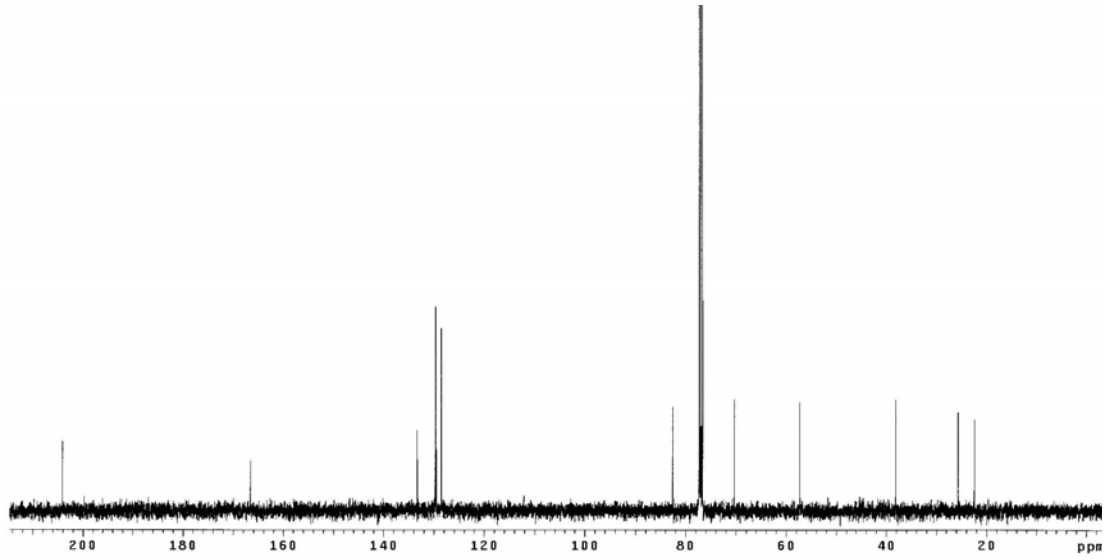
^{13}C NMR of **4.26a**



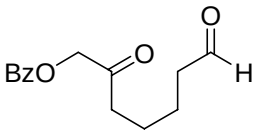
Benzoic acid 2-formyl-1-hydroxycyclopentylmethyl ester 4.26b. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (d, *J* = 2.0 Hz, 1H), 8.03 (dd, *J* = 6.5, 1.4 Hz, 2H), 7.58 (tt, *J* = 7.5 Hz, 1.0 1H), 7.46 (t, *J* = 8.2 Hz, 2H), 4.49 (A part of AB system, *J* = 11.4 Hz, 1H), 4.42 (B part of AB system, *J* = 11.4 Hz, 1H), 3.08 (s, 1H), 2.80 (t,d, *J* = 8.9, 2.0 Hz, 1H), 2.20 (m, 1H), 2.01 (m, 2H), 1.87 (t, *J* = 6.5, 2H), 1.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.1, 166.6, 133.3, 129.7, 129.5, 128.5, 82.6, 70.3, 57.3, 38.1, 25.7, 22.4. FTIR (NaCl): 3452, 3056, 2963, 1720, 1445, 1270, 1102, 1017 cm^{-1}. HRMS: calcd for $C_{14}H_{17}O_4$ [M+1] 249.11268; found 249.11298.



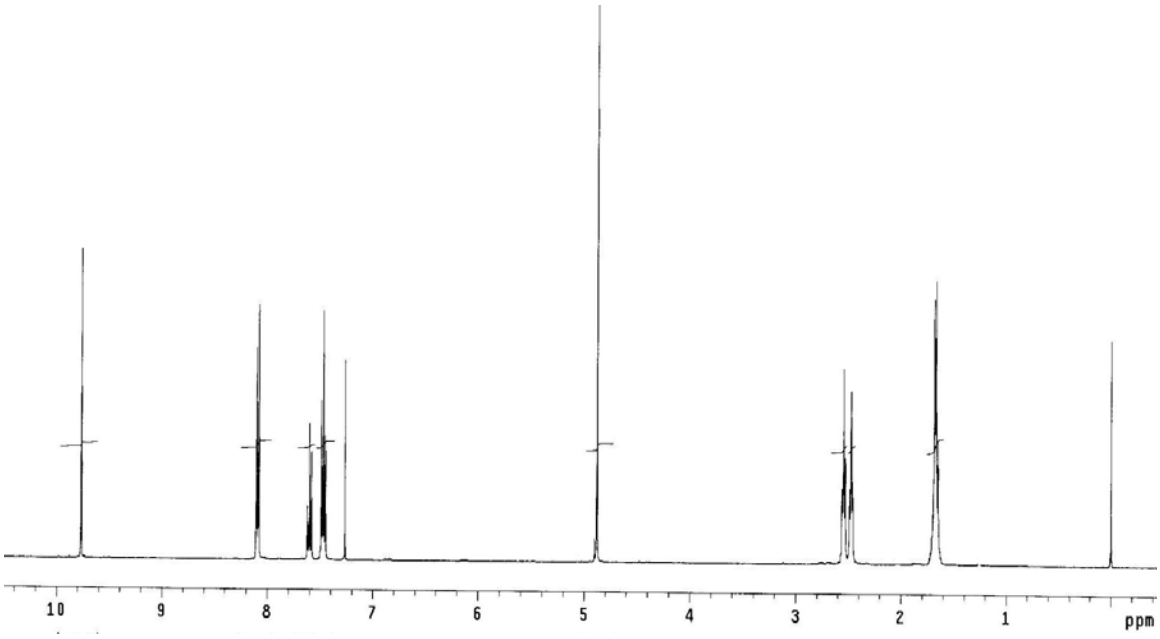
^{1}H NMR of **4.26b**



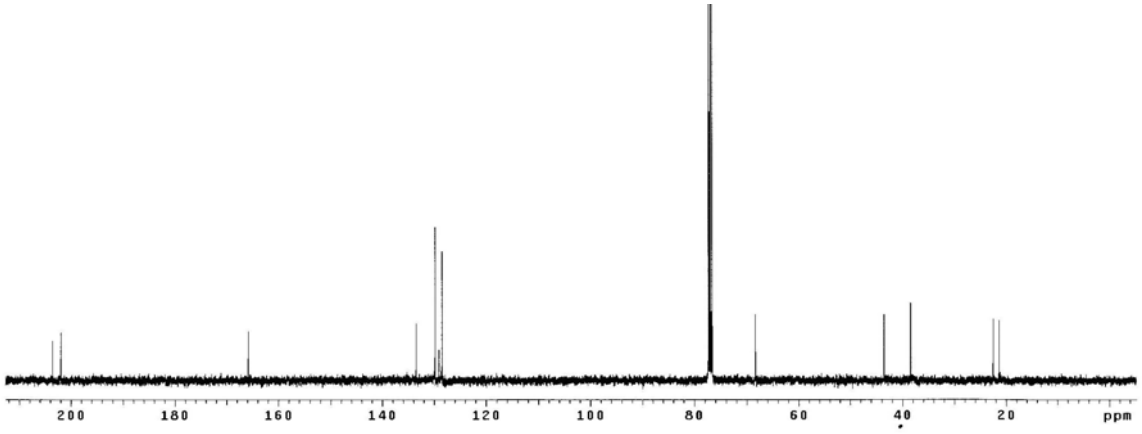
^{13}C NMR of **4.26b**



Benzoic acid 2.7-dioxo-heptyl ester 4.26c. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (t, *J* = 1.7 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.9, 2H), 4.87 (s, 2H), 2.54 (t, *J* = 7.2, 2H), 2.46 (m, 2H), 1.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.6, 202.0, 165.8, 133.4, 129.8, 129.1, 128.5, 68.4, 43.5, 38.4, 22.5, 21.4. FTIR (NaCl): 2935, 2881, 2722, 1720, 1596, 1448, 1274, 1177, 1099, 1033, 920 cm^{-1}. HRMS calculated [M+1] for $C_{14}H_{17}O_4$ 249.11268; found 249.11195.



^{1}H NMR of **4.26c**



^{13}C NMR of **4.26c**

4.6 References

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Vita

Phillip Kimaiyo Koech was born in Eldoret, Kenya on January 13, 1974, the son of William Kipkoech Rono and Christine Jemeli Rono. After graduating from Kapsabet Boys High School, Kapsabet, Kenya, in 1993, he taught at Cengalo Secondary School, Burnt Forest, Kenya until November 1995 when he joined Kenyatta University, Nairobi, Kenya where he graduated with a degree of Bachelor of Education in Chemistry and Mathematics in October of 1999. He taught at Sochoi Secondary School, Lessos, Kenya from July of 1999 to November of 2000. In January of 2001, he entered the Graduate School at Central Michigan University, Mt. Pleasant, MI. Under the direction of Professor Thomas Delia he was awarded the Graduate Research Grant. He graduated with a degree of Master of Science in Chemistry in December of 2002. In August 2002 he joined the Graduate School at the University of Texas at Austin. Under the direction of Professor Michael J. Krische, in May of 2005, he was awarded the Welch Summer Research Fellowship from the Department of Chemistry.

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